A Focus on CKD and Heart Diseases

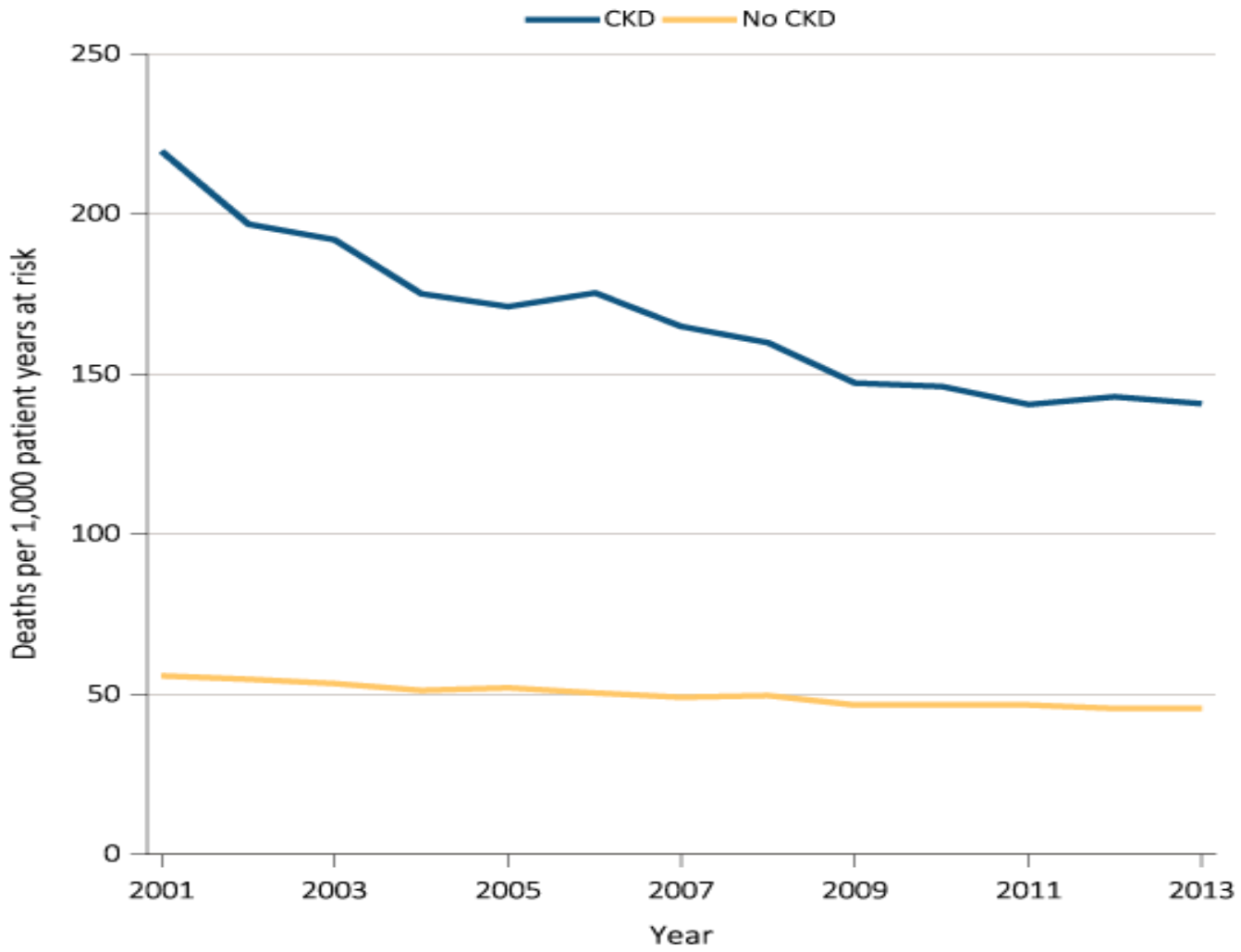
By
Mohammed Kamal Nassar
Assistant Lecturer of Internal Medicine (Nephrology)
Mansoura University

CKD-CVD: Magnitude of the Problem



USRDS 2015 Annual Data Report

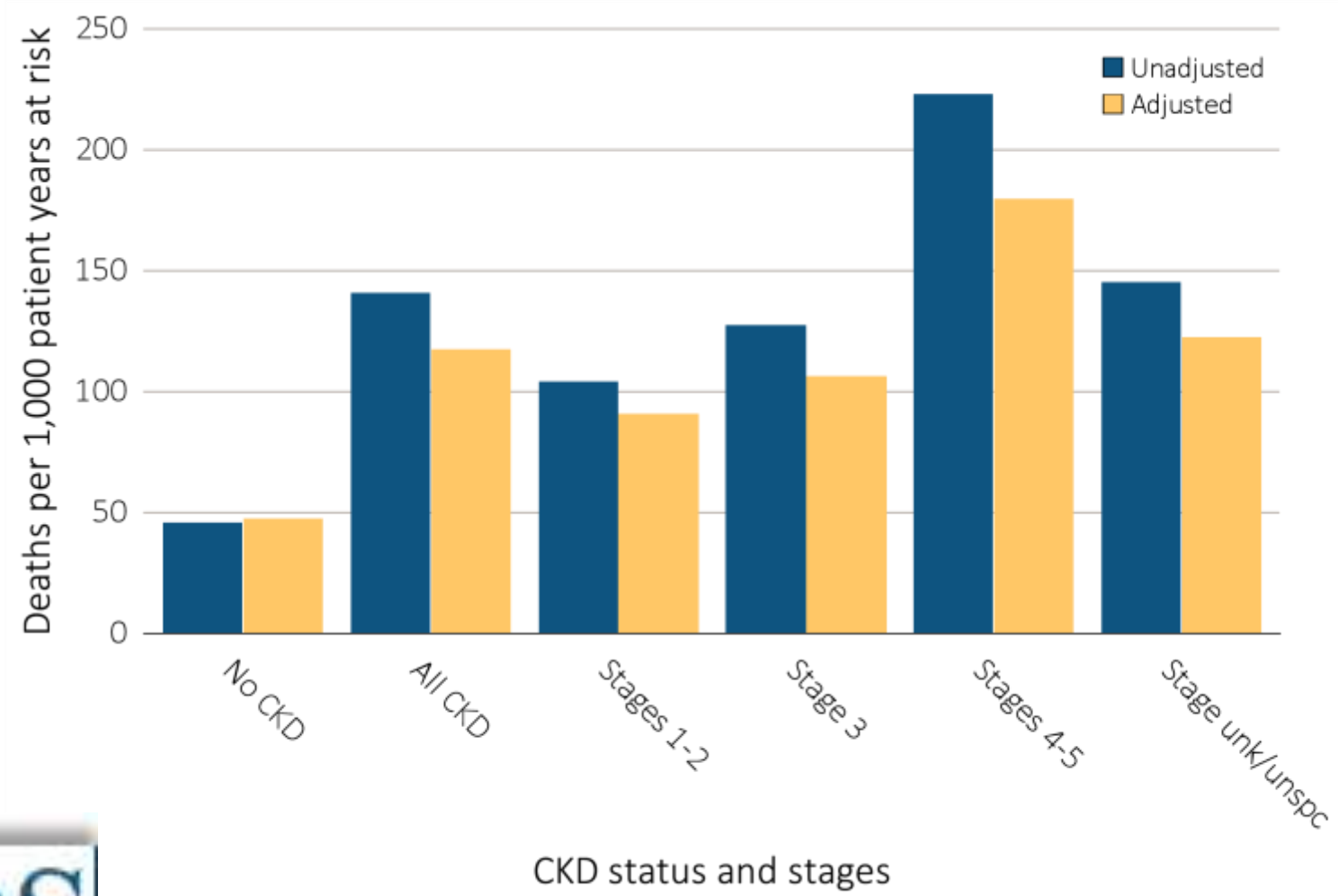
All cause mortality



USRDS 2015 Annual Data Report

USRDS
UNITED STATES RENAL DATA SYSTEM

Mortality by CKD status and stage

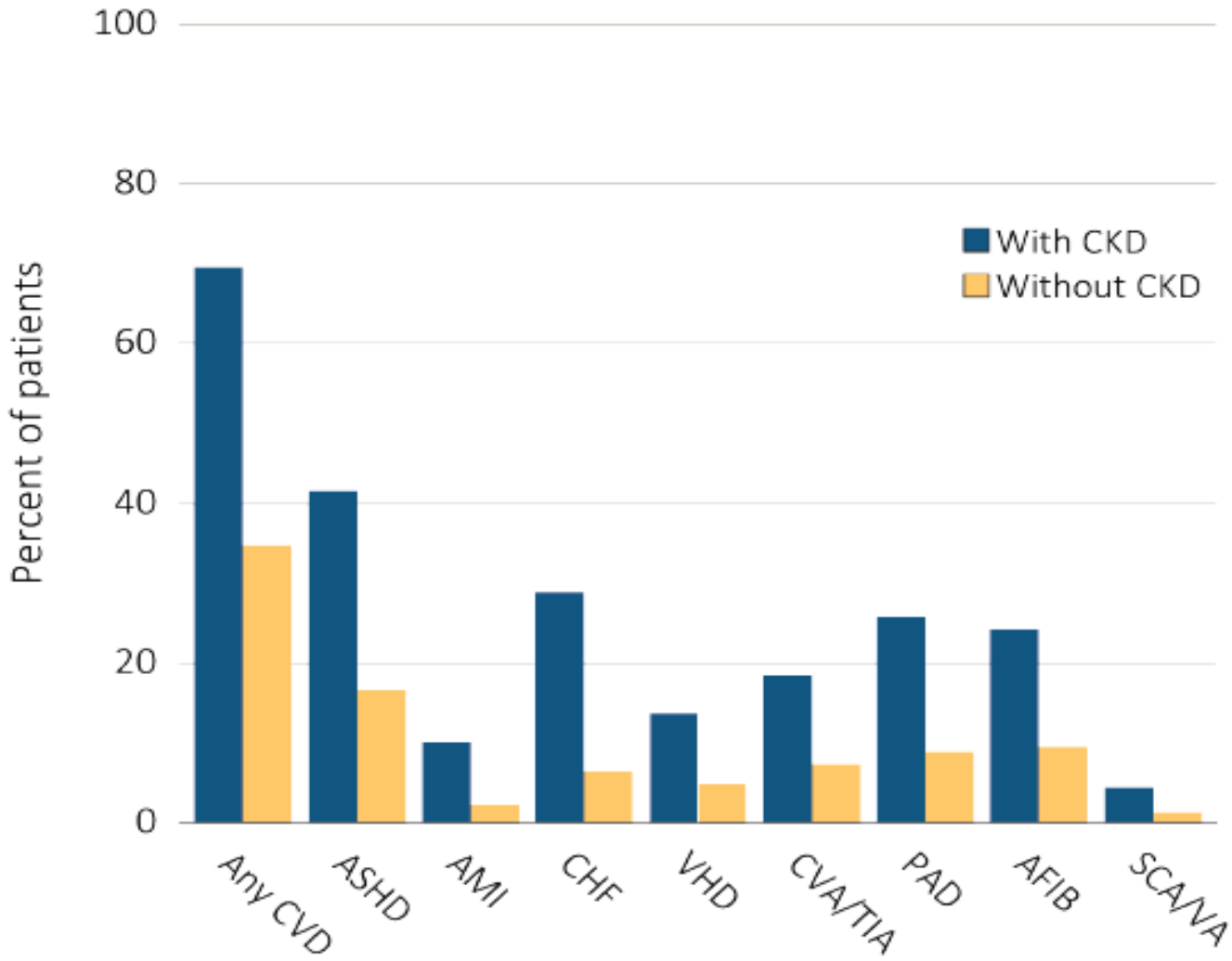


~40% Cardiac Causes

USRDS
UNITED STATES RENAL DATA SYSTEM

USRDS 2015 Annual Data Report

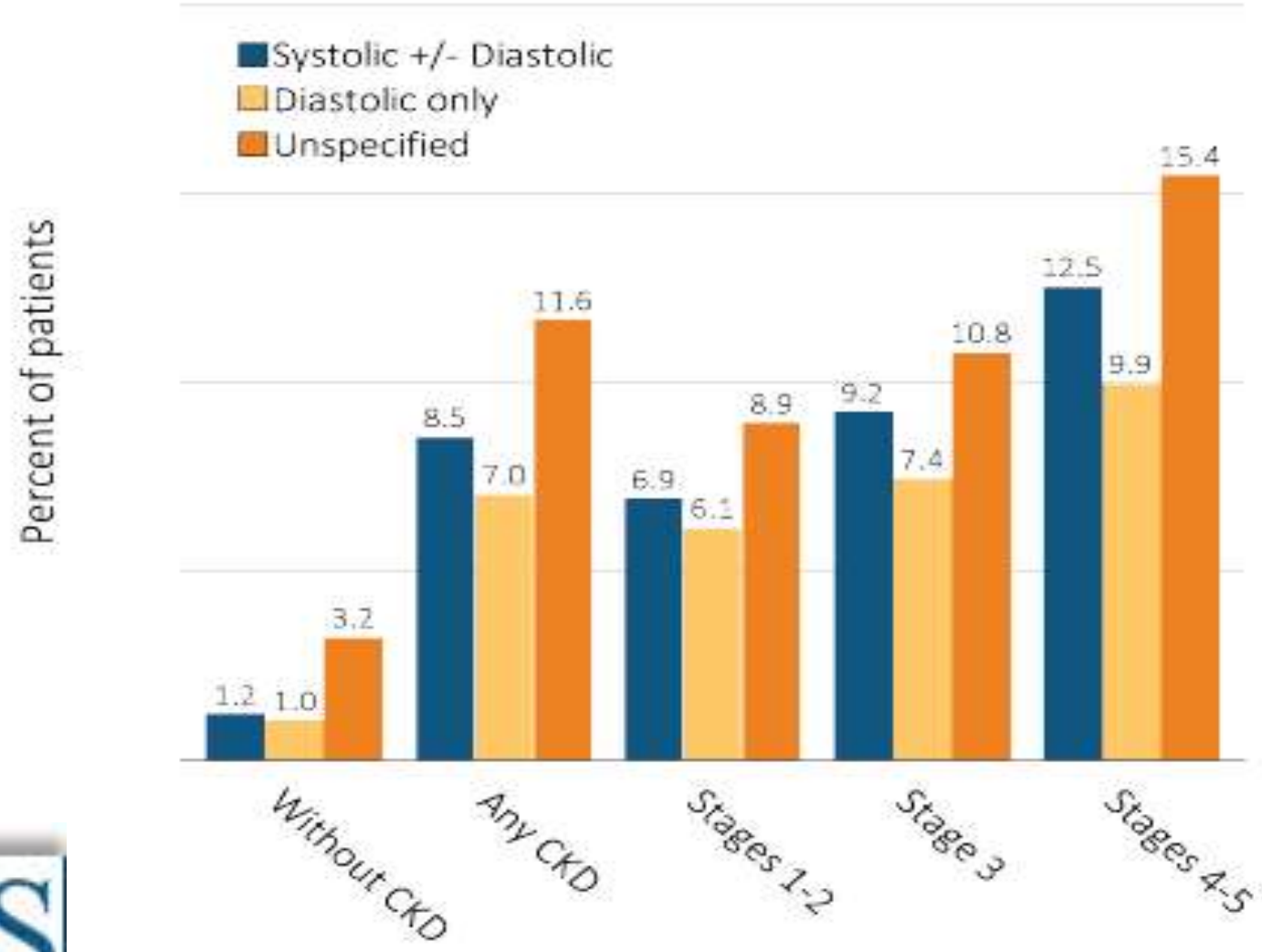
Prevalence of CVD



USRDS 2015 Annual Data Report

USRDS
UNITED STATES RENAL DATA SYSTEM

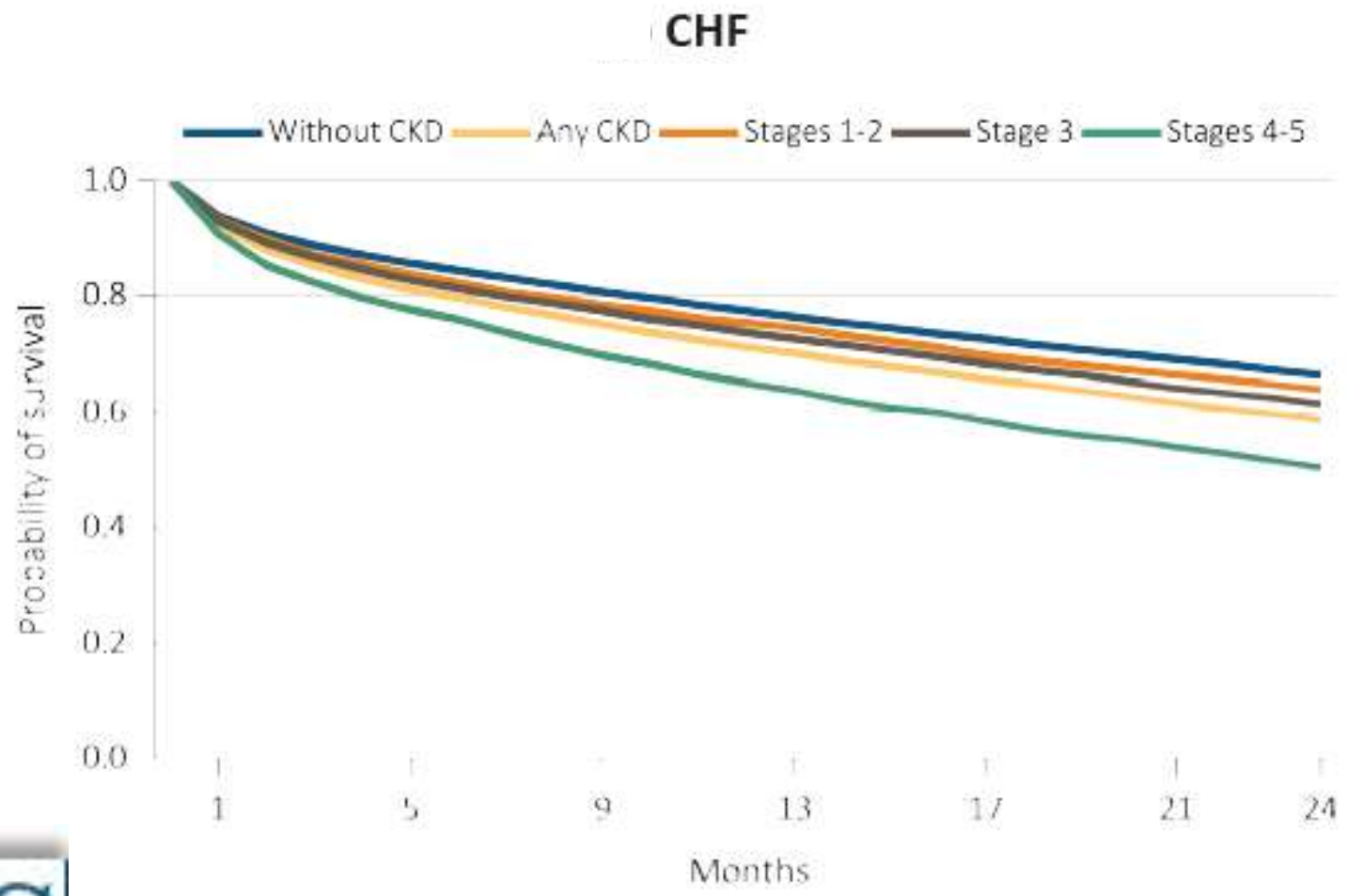
Heart failure with and without CKD



USRDS
UNITED STATES RENAL DATA SYSTEM

USRDS 2015 Annual Data Report

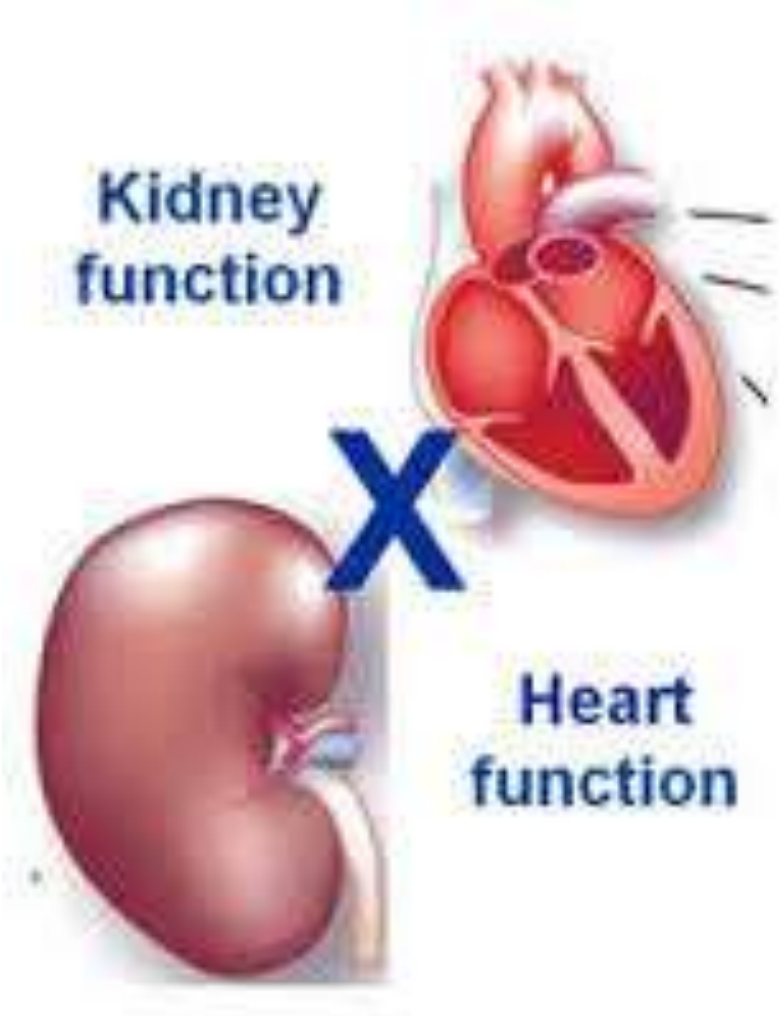
Survival of CHF with and without CKD



USRDS
UNITED STATES RENAL DATA SYSTEM

USRDS 2015 Annual Data Report

Cardiorenal Syndromes

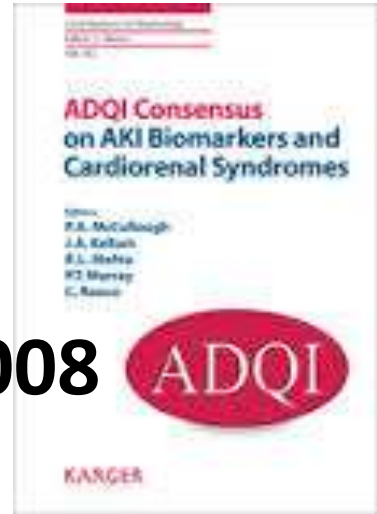


Definition

Disorders of the heart and kidneys whereby acute or chronic dysfunction in one organ may induce acute or chronic dysfunction of the other organ.

J Am Coll Cardiol. 2008;52(19):1527–1539.

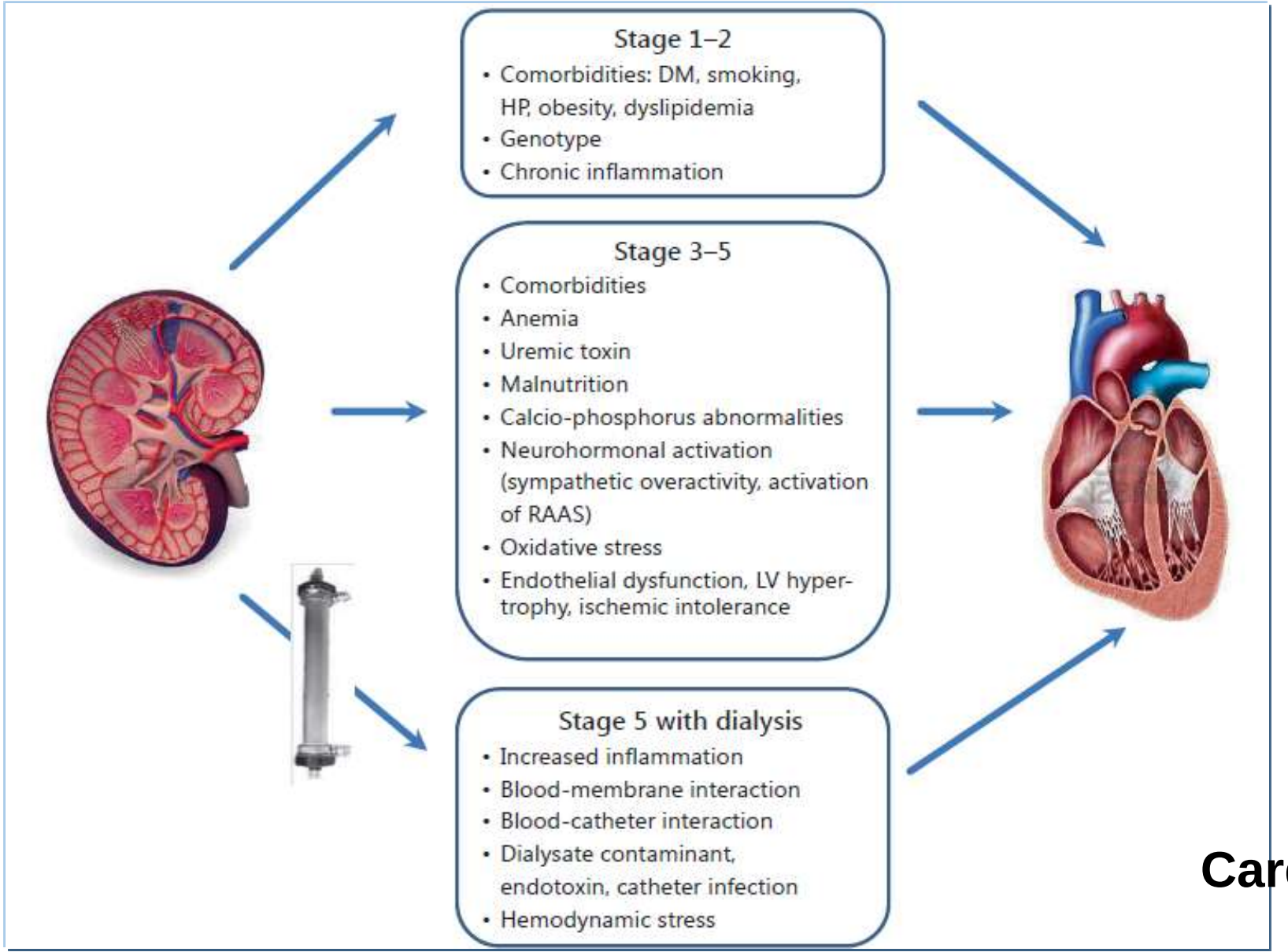
2008



Cardio-Renal syndromes

CRS Type I (Acute Cardiorenal Syndrome) Abrupt worsening of cardiac function (e.g. acute cardiogenic shock or acutely decompensated congestive heart failure) leading to acute kidney injury
CRS Type II (Chronic Cardiorenal Syndrome) Chronic abnormalities in cardiac function (e.g. chronic congestive heart failure) causing progressive and potentially permanent chronic kidney disease
CRS Type III (Acute Renocardiac Syndrome) Abrupt worsening of renal function (e.g. acute kidney ischaemia or glomerulonephritis) causing acute cardiac disorder (e.g. heart failure, arrhythmia, ischemia)
CRS Type IV (Chronic Renocardiac Syndrome) Chronic kidney disease (e.g. chronic glomerular or interstitial disease) contributing to decreased cardiac function, cardiac hypertrophy and/or increased risk of adverse cardiovascular events
CRS Type V (Secondary Cardiorenal Syndrome) Systemic condition (e.g. diabetes mellitus, sepsis) causing both cardiac and renal dysfunction

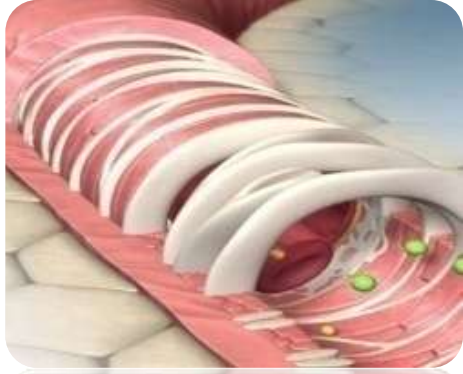
CRS Type 4



Cardiorenal Med 2013;3:63–70

Vascular Calcification

Overview



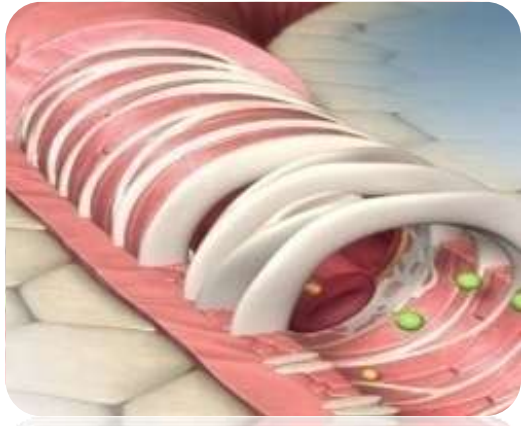
- Vascular calcification (VC) is highly correlated with cardiovascular morbidity and mortality, and linked to aging, diabetes and CKD.

- The prevalence of VC increases steadily through the stages of CKD peaking in CKD stage 5D patients.

- The KDIGO guidelines suggest that CKD Stage 3–5D patients with known vascular/valvular calcification need to 'be considered as having the highest possible cardiovascular risk'.

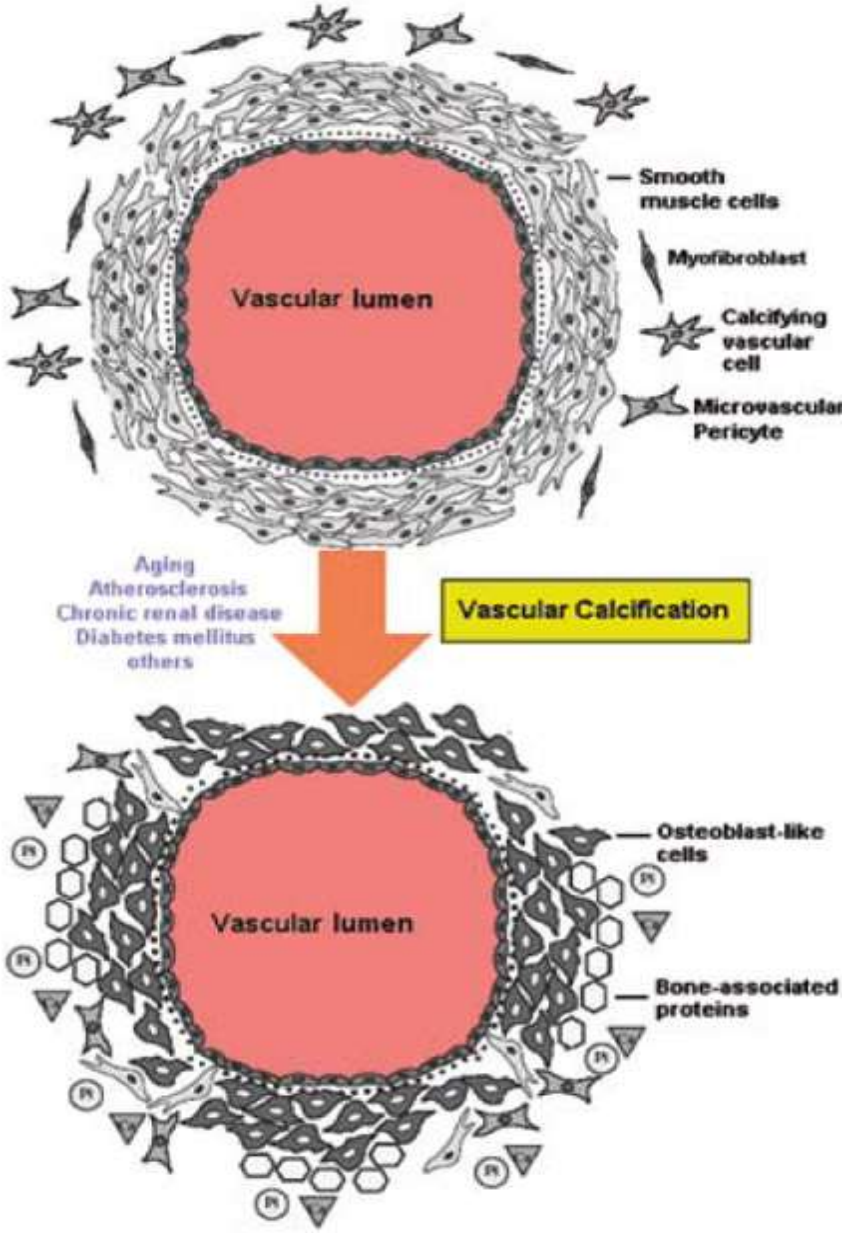
J Hypertens 2010; 28: 163–169

Overview





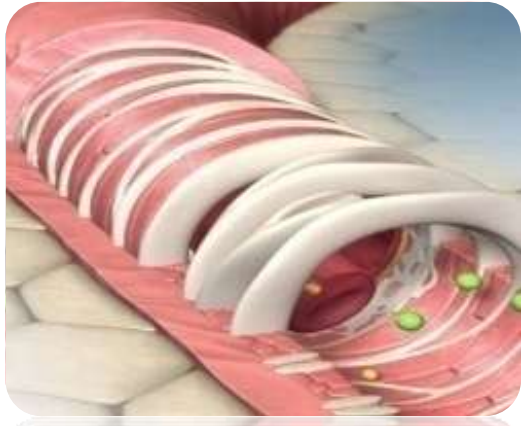
Calcific uremic arteriolopathy





Calcific Aortic valve

Overview

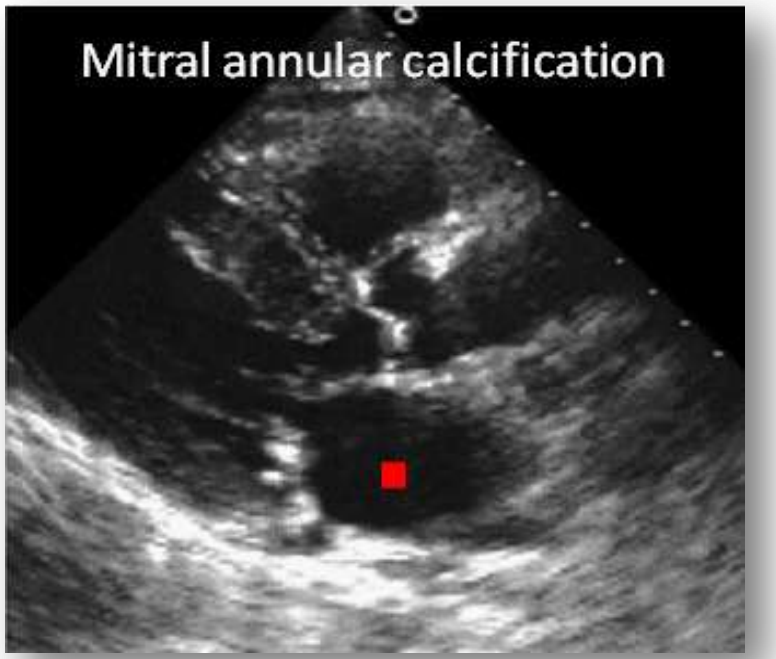




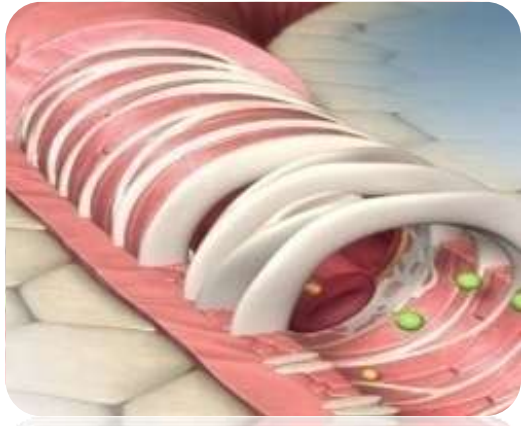
Digital Arteries Calcification

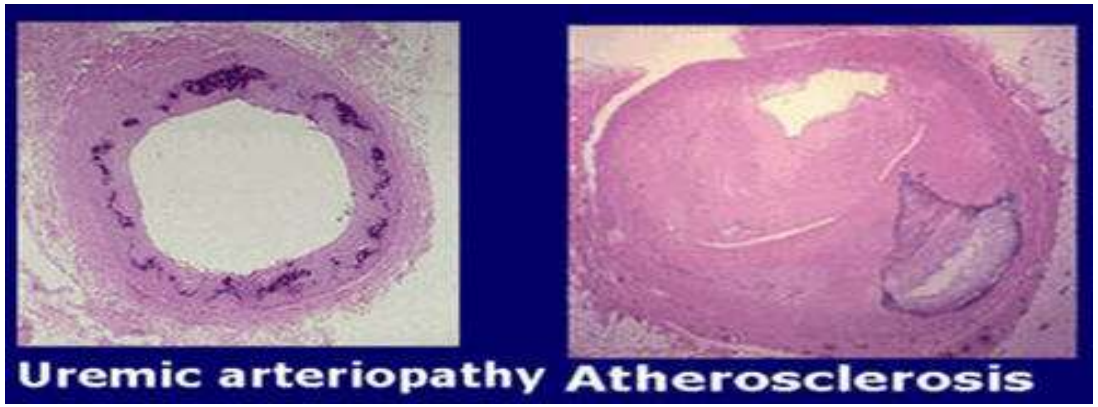


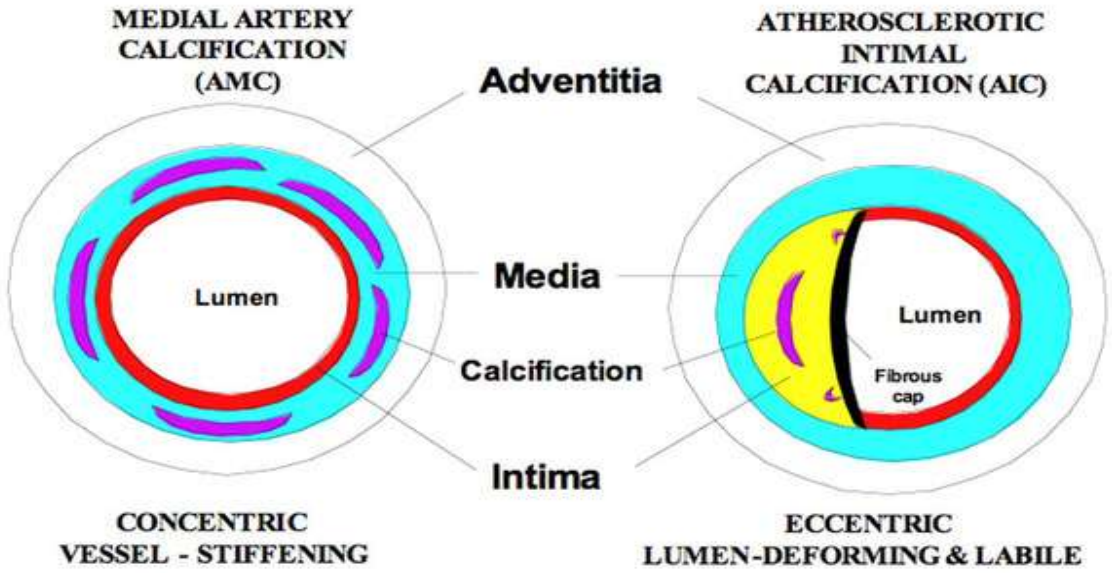
Aortic Calcifications



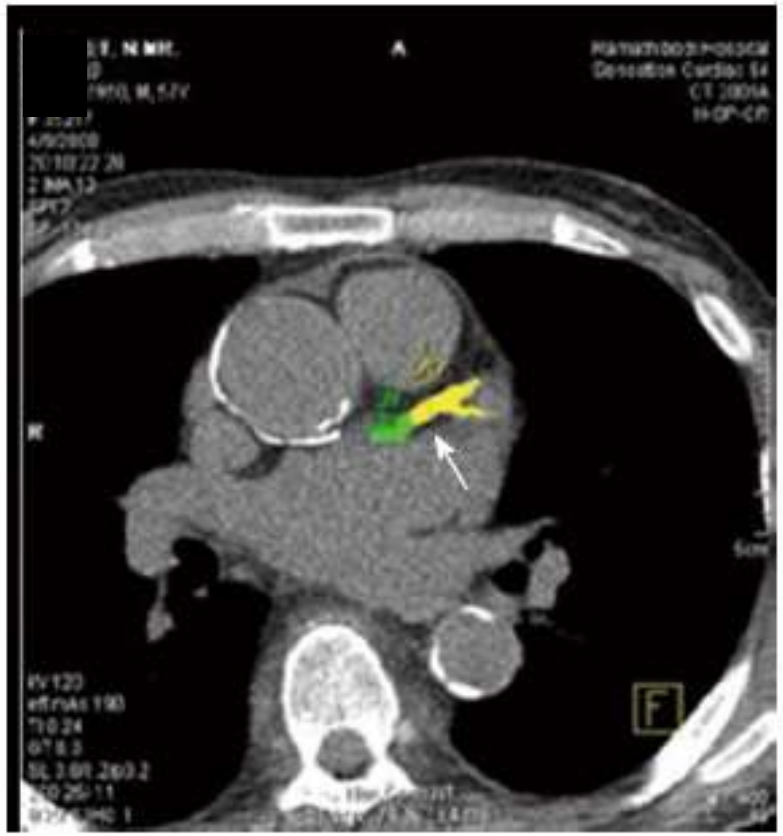
Types of Vascular Calcifications in CKD







Diagnosis

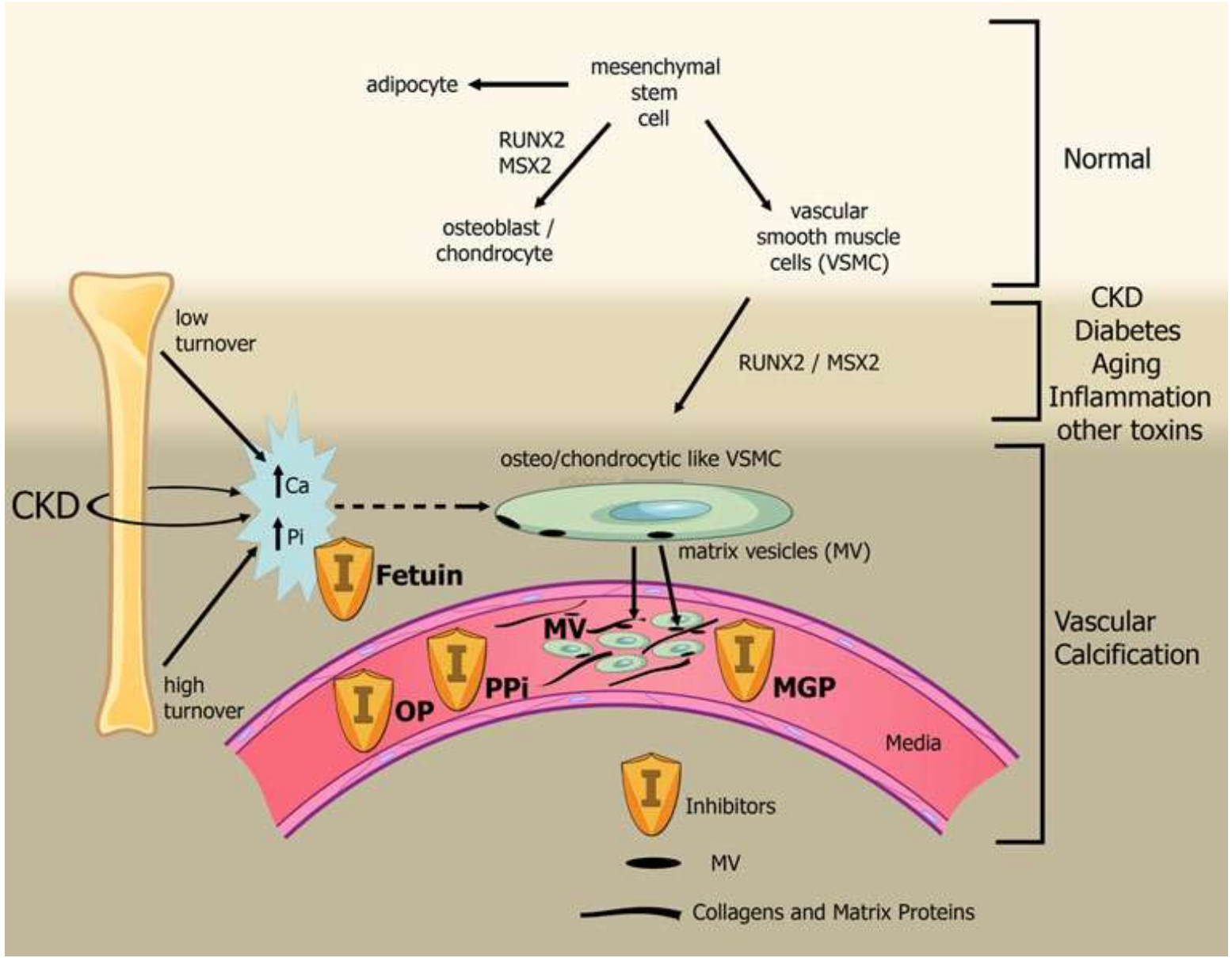




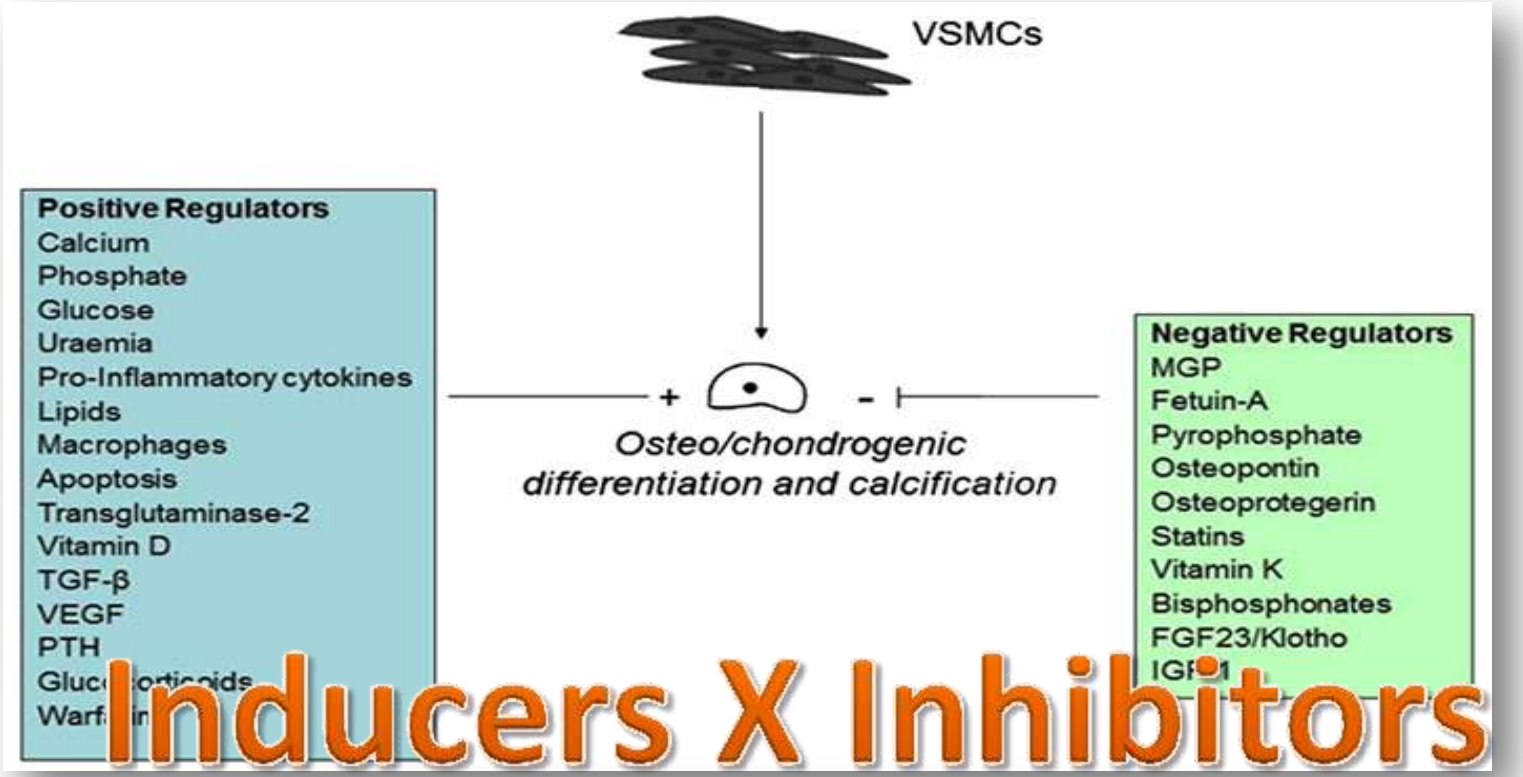


World J Nephrol 2012 6; 1(2): 43-53

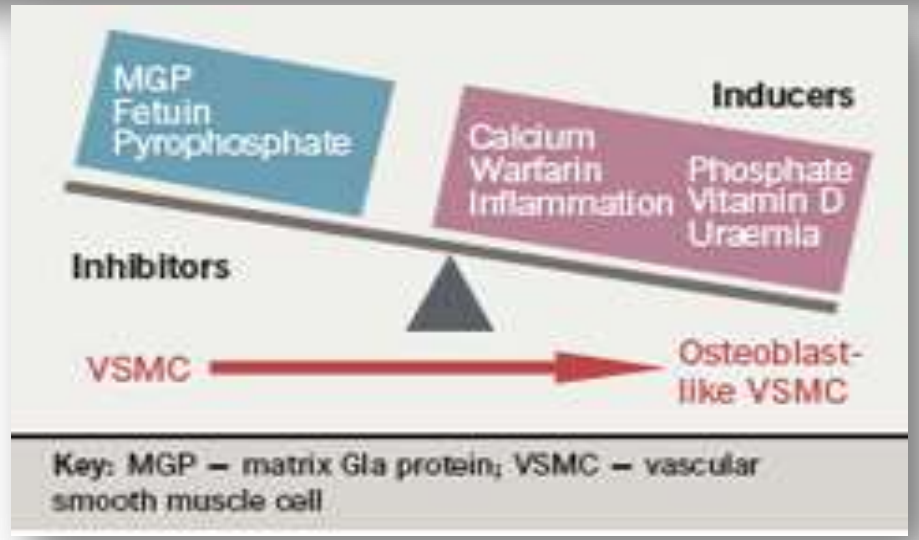
Pathogenesis



J Am Soc Nephrol, 2008.
19(2): p. 213-6



Inducers X Inhibitors



1. PO4

REVIEW

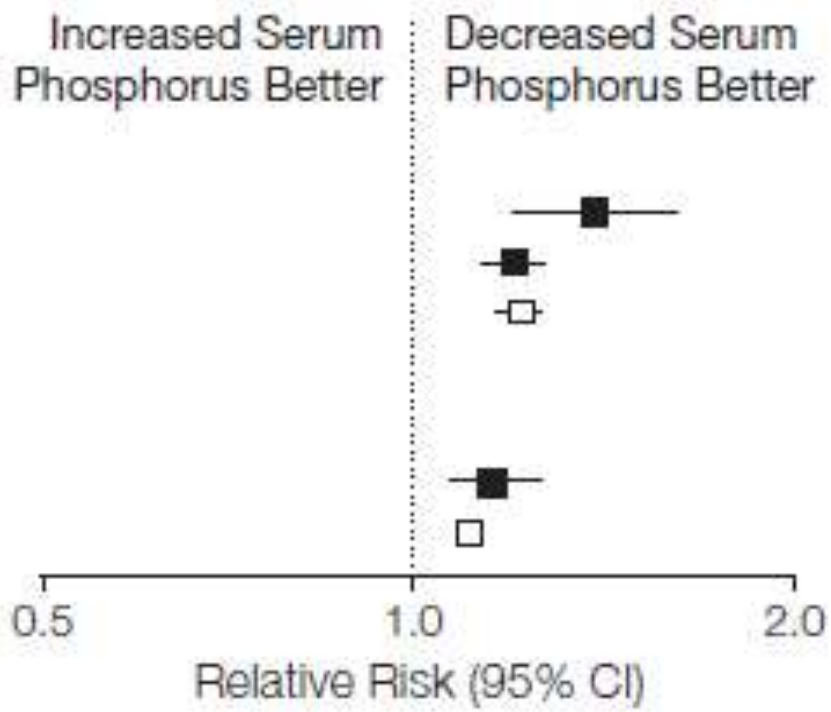
Serum Levels of Phosphorus, Parathyroid Hormone, and Calcium and Risks of Death and Cardiovascular Disease in Individuals With Chronic Kidney Disease

A Systematic Review and Meta-analysis

JAMA, March 16, 2011—Vol 305, No. 11

PO4 and CV morbidity

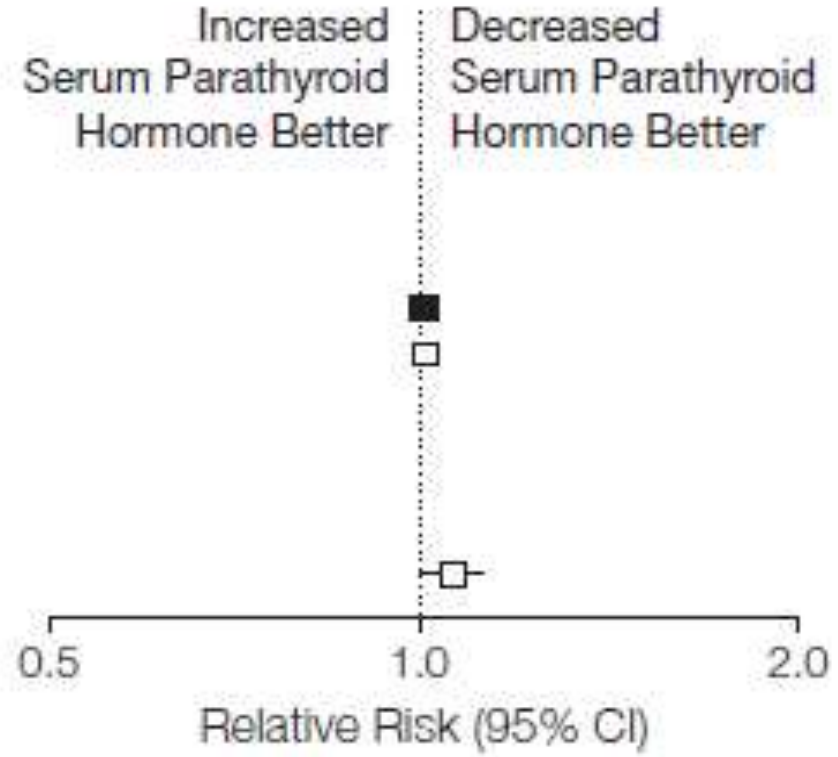
Phosphorus	No. of Cohorts	No. of Participants	Relative Risk (95% CI) Per Unit Increase
All-cause mortality			
Adequate adjustment	3	4651	1.35 (1.16-1.57)
Partial adjustment	10	87 694	1.16 (1.09-1.23)
All studies combined	13	92 345	1.18 (1.12-1.25)
Cardiovascular mortality			
Adequate adjustment	1	17 326	Not estimable
Partial adjustment	2	5881	1.14 (1.05-1.24)
All studies combined	3	23 207	1.10 (1.06-1.13)



JAMA, March 16, 2011—Vol 305, No. 11

PTH and CV morbidity

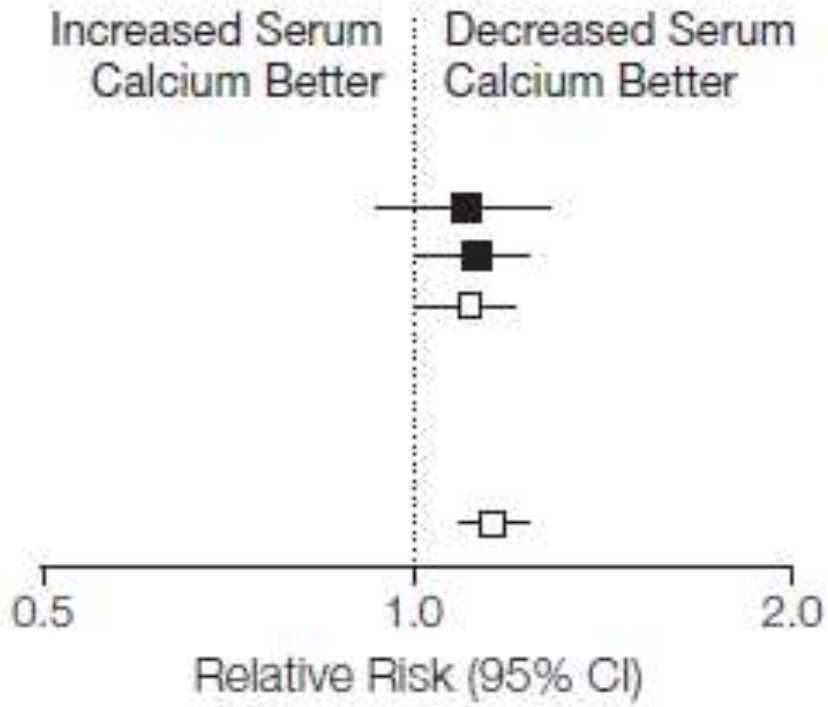
Parathyroid hormone	No. of Cohorts	No. of Participants	Relative Risk (95% CI)
All-cause mortality			
Adequate adjustment	1	17 326	Not estimable
Partial adjustment	3	83 732	1.01 (0.99-1.03)
All studies combined	4	101 058	1.01 (1.00-1.02)
Cardiovascular mortality			
Adequate adjustment	1	17 326	Not estimable
Partial adjustment	1	5041	Not estimable
All studies combined	2	22 367	1.05 (0.99-1.11)



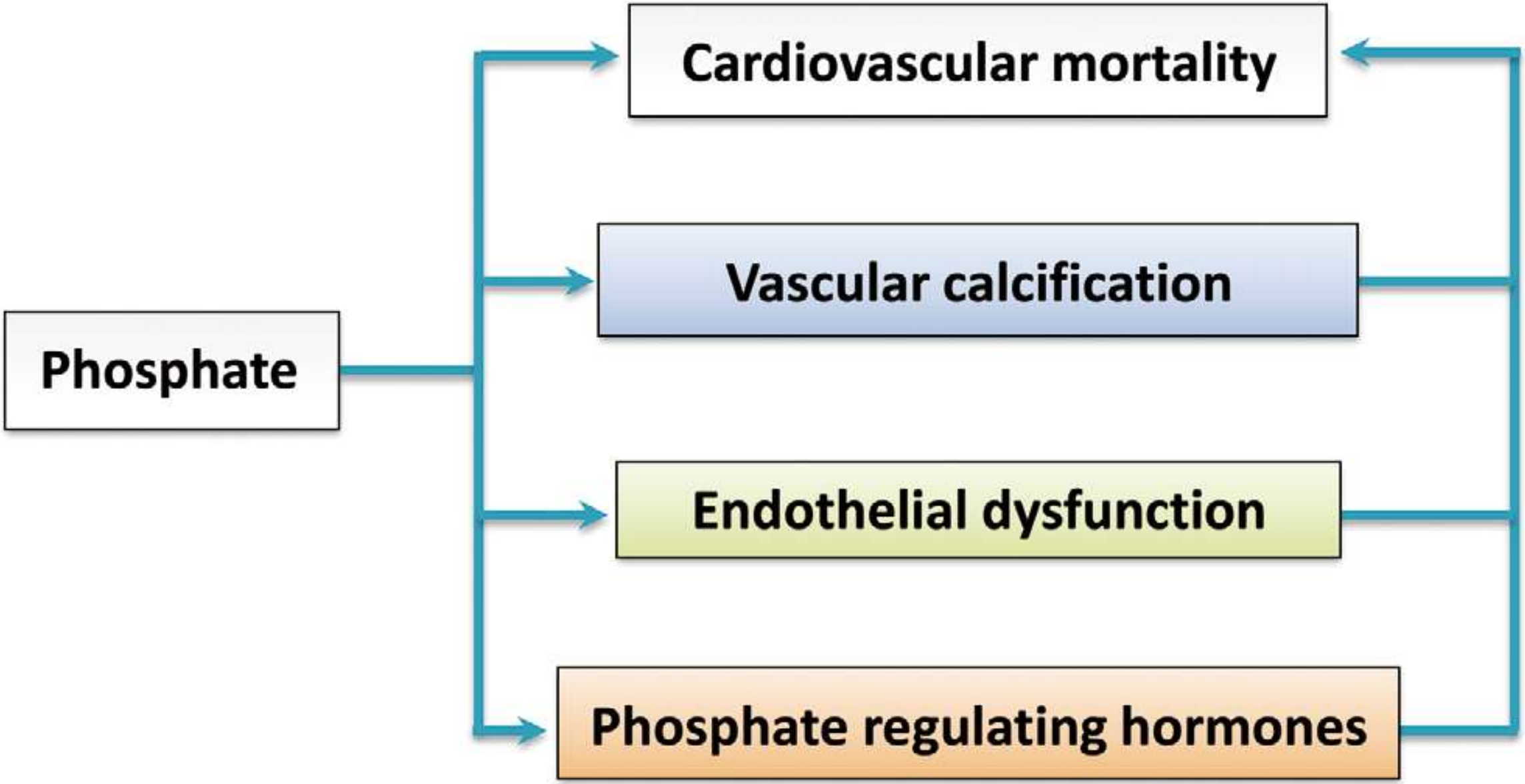
JAMA, March 16, 2011—Vol 305, No. 11

Ca and CV morbidity

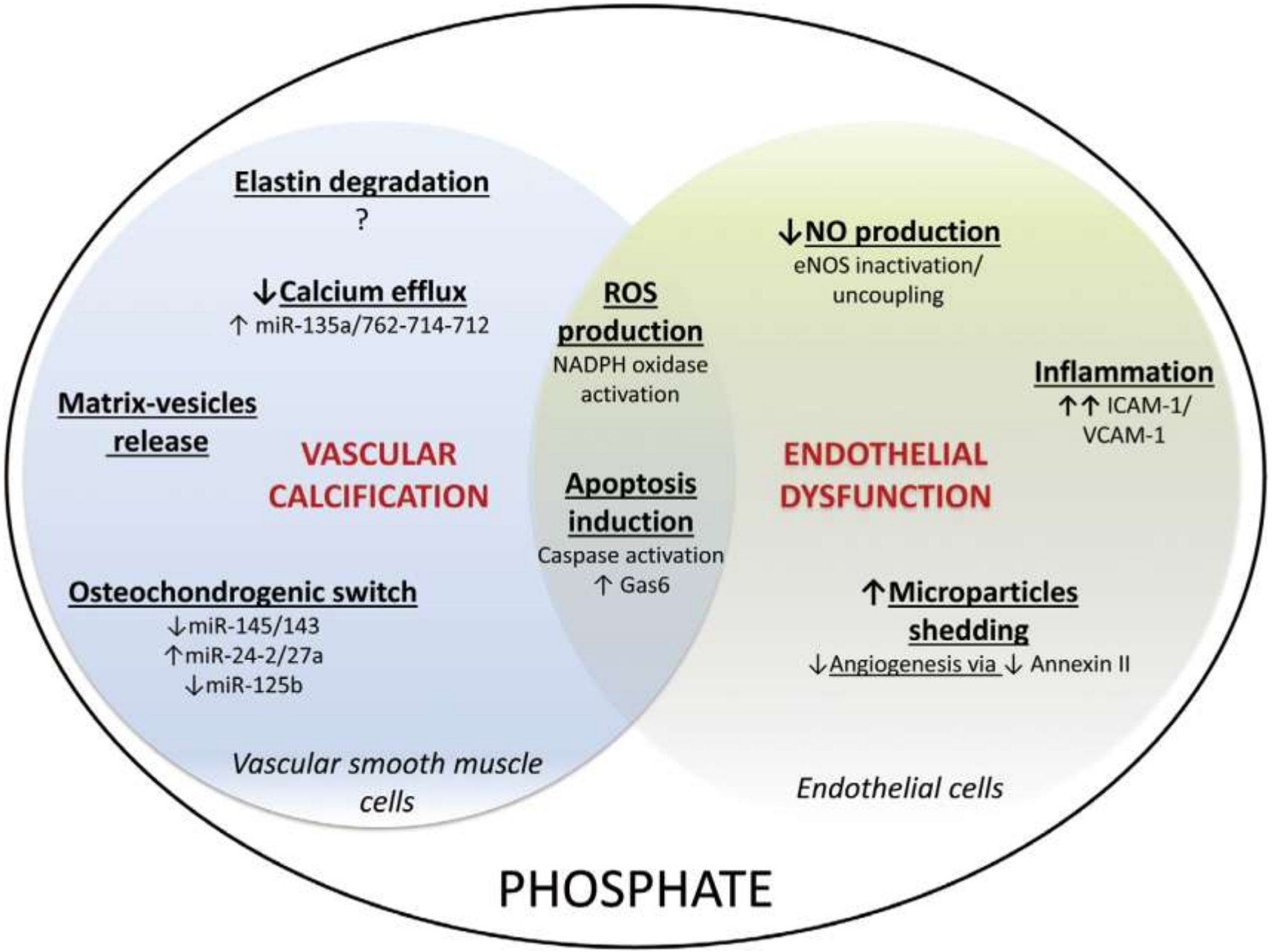
Calcium	No. of Cohorts	No. of Participants	Relative Risk (95% CI)
All-cause mortality			
Adequate adjustment	2	22 367	1.07 (0.91-1.24)
Partial adjustment	6	83 789	1.09 (0.99-1.20)
All studies combined	8	106 156	1.08 (1.00-1.16)
Cardiovascular mortality			
Adequate adjustment	1	17 326	Not estimable
Partial adjustment	1	5041	Not estimable
All studies combined	2	22 367	1.15 (1.08-1.23)



JAMA, March 16, 2011—Vol 305, No. 11

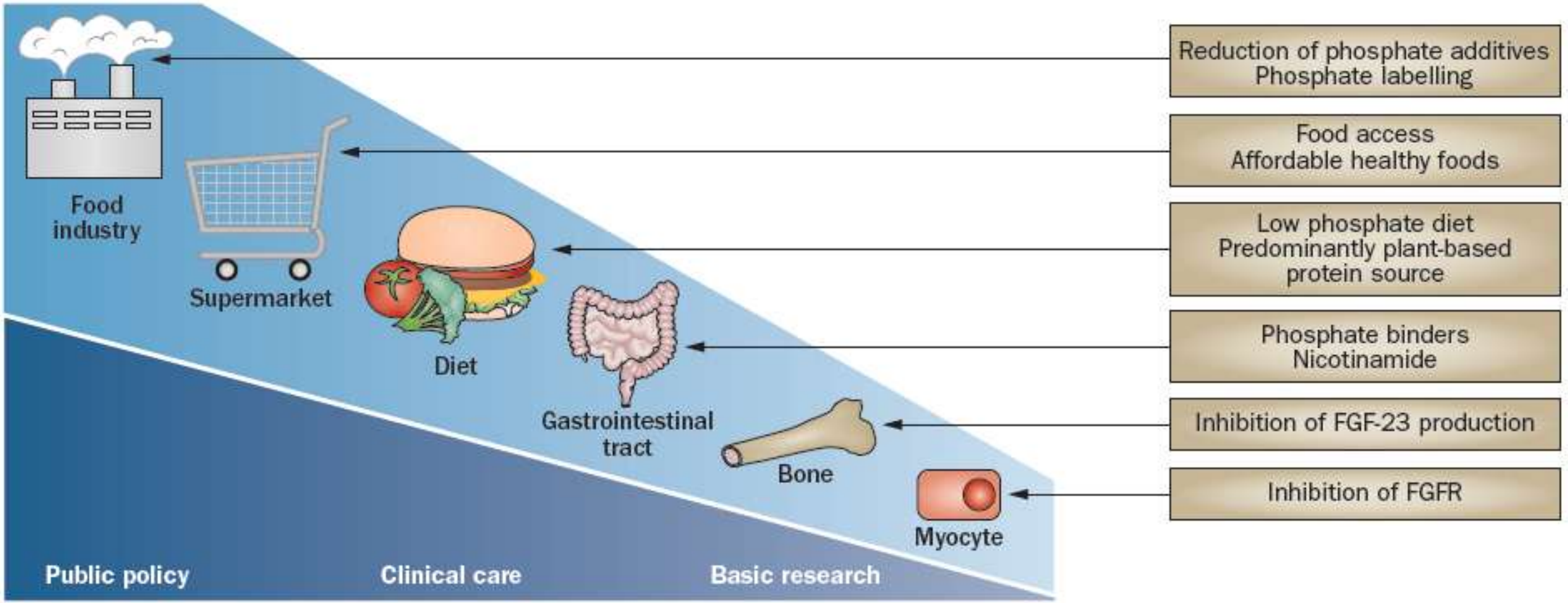


Circ J 2014; 78: 2339 – 2346



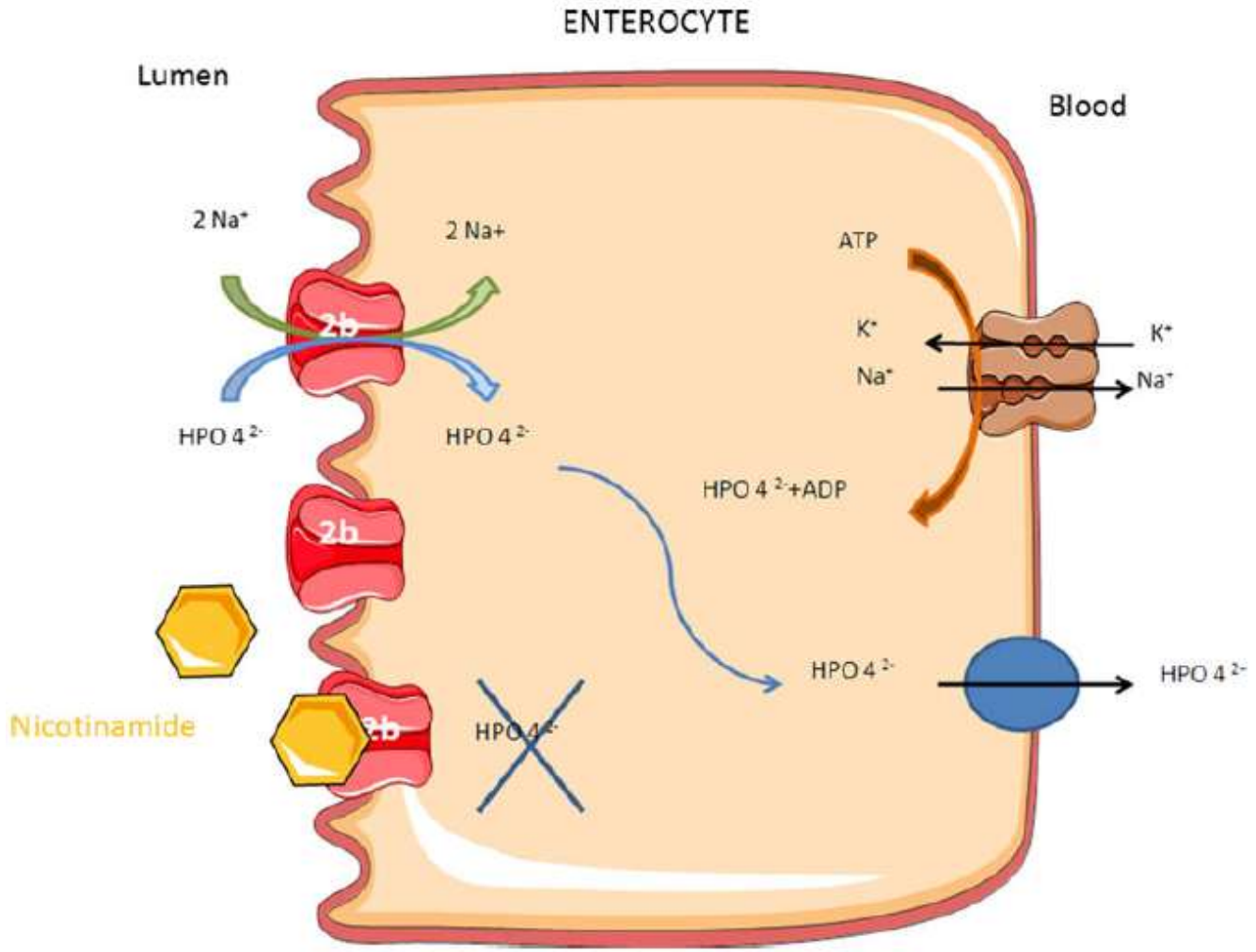
***Circ J* 2014; 78: 2339 – 2346**

Interventions targeting phosphate homeostasis



Nat. Rev. Nephrol. 10, 268–278 (2014)

Nicotinamide



Drugs R D (2013) 13:165–173

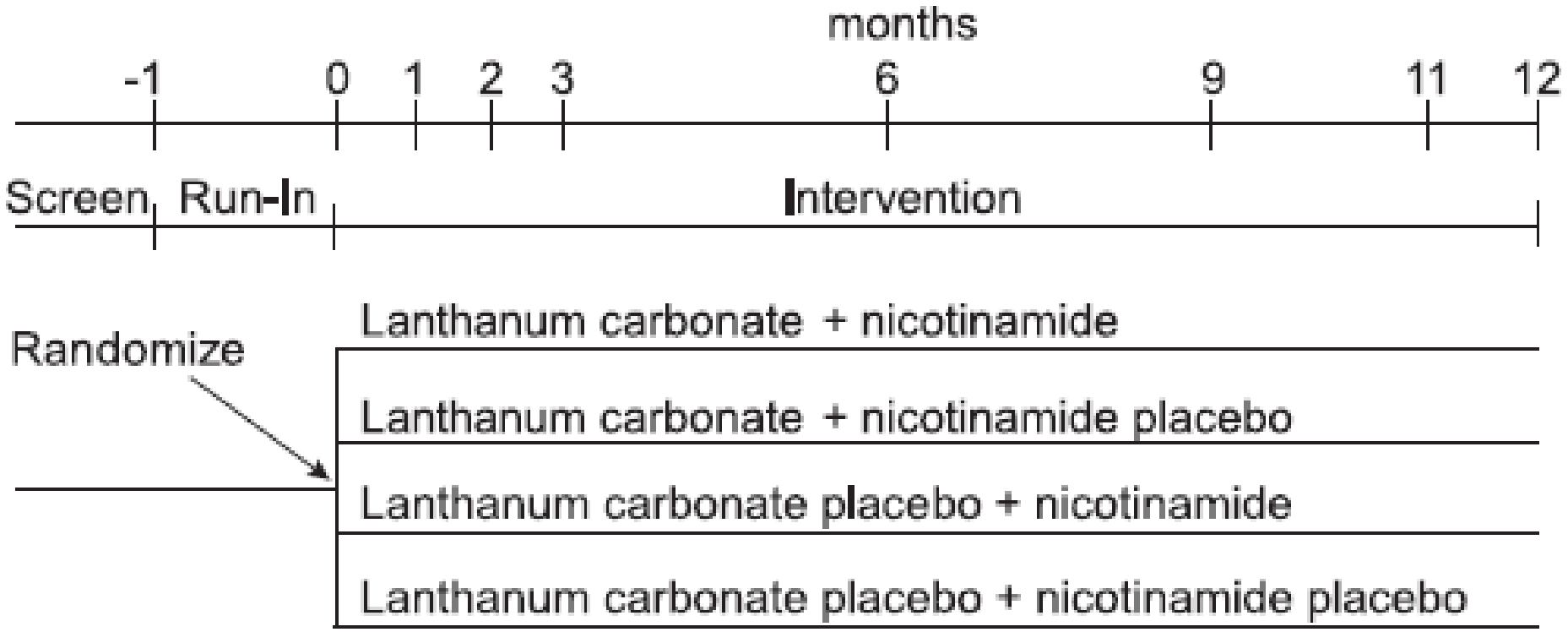
References	Type of study	Number of ESRD patients	Number of patients on NAM	NAM dose (mg/day)	Time exposed (weeks)	Change in blood phosphate (%)	Phosphate binders
Takahashi et al. [48]	Open-label	65	65	500–1,750	12	−21	Calcium carbonate
Cheng et al. [49]	Prospective, double-blind, placebo-controlled, randomized, cross-over	33	25	500–1,500	8	−15	Phosphate binder
Young et al. [50]	Prospective, double-blind, placebo-controlled, randomized	15	8	750–1,250	8	−12	Phosphate binder
Shahbazian et al. [51]	Prospective, double-blind, placebo-controlled, randomized	48	24	500–1,000	8	−21	Phosphate binder
Vasantha et al. [52]	Prospective, open-label	30	30	750	8	−34	None

Thrombocytopenia

Drugs R D (2013) 13:165–173

The COMBINE study

Enrollment began in March 2015, and results are anticipated by 2018

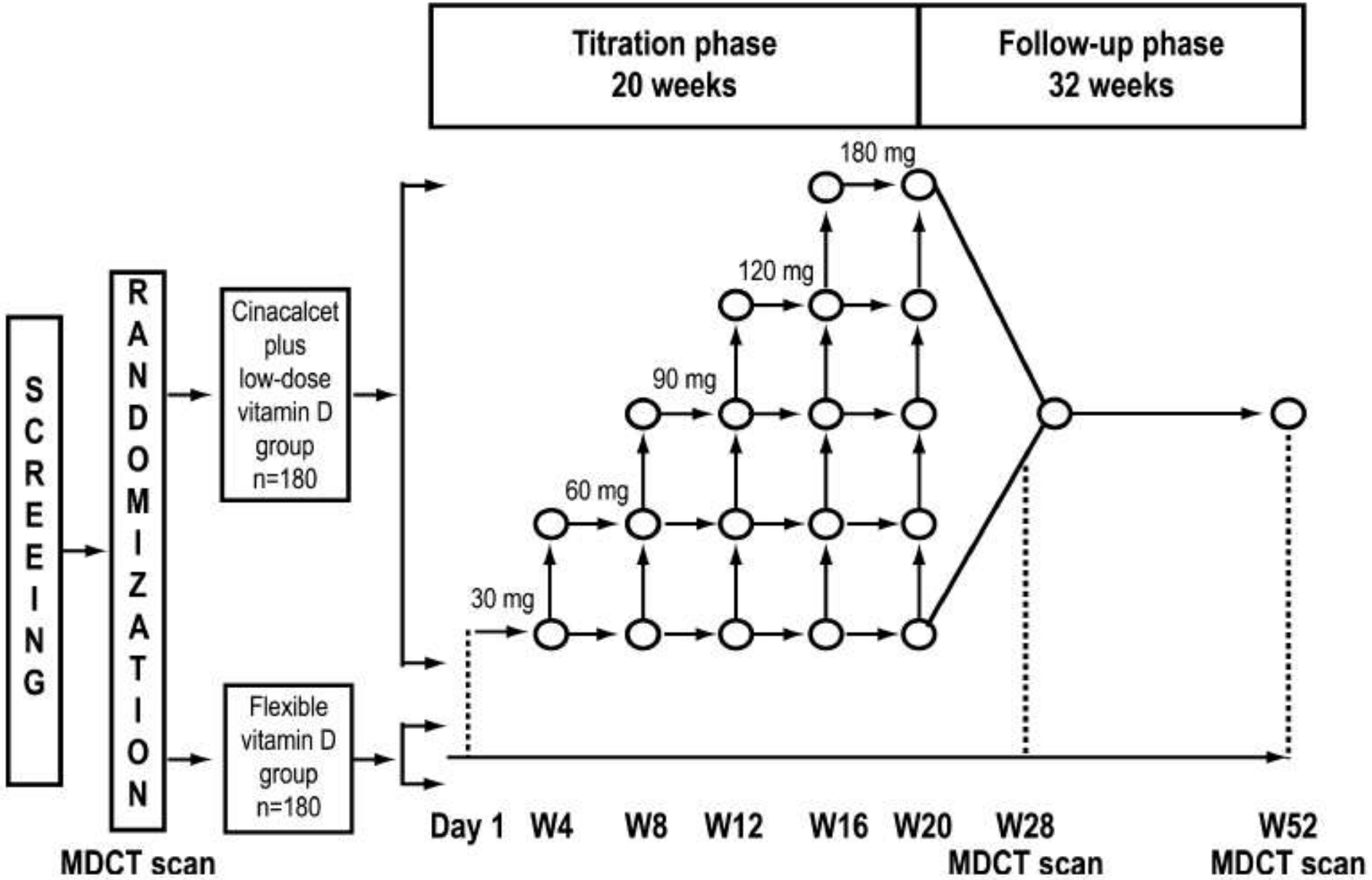


JASN May 12, 2015

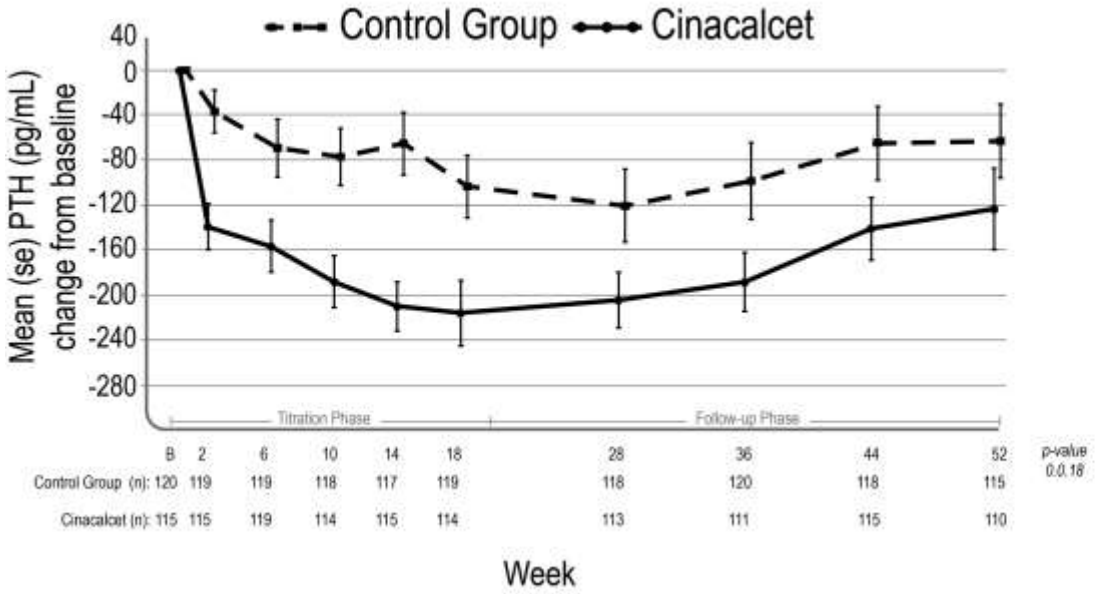
2. PTH
Calcimimetics

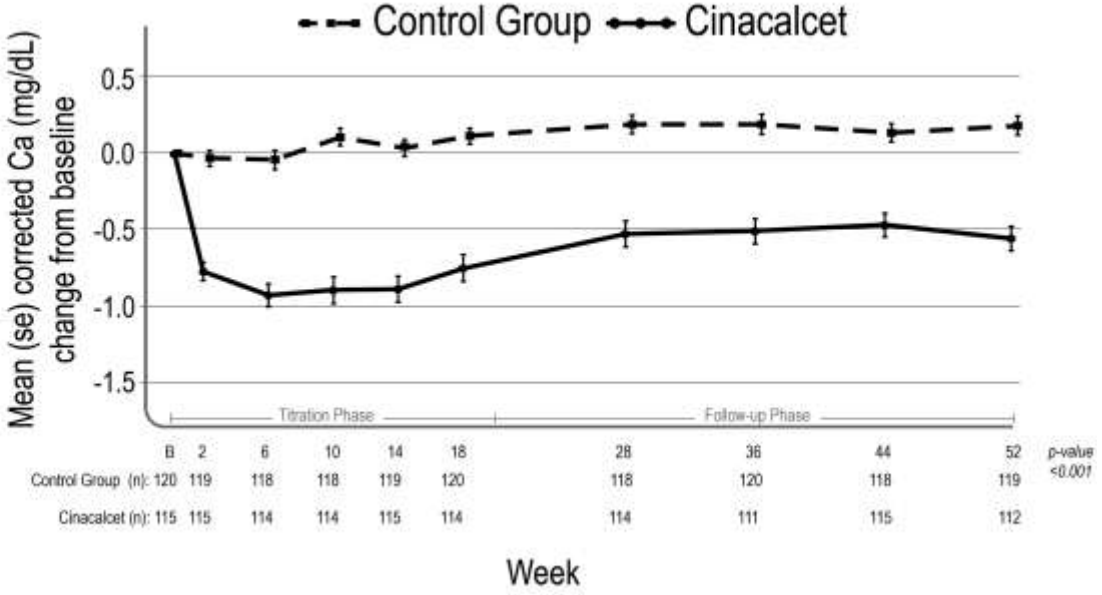
Nephrol Dial Transplant (2011) 26: 1327–1339
doi: 10.1093/ndt/gfq725
Advance Access publication 8 December 2010

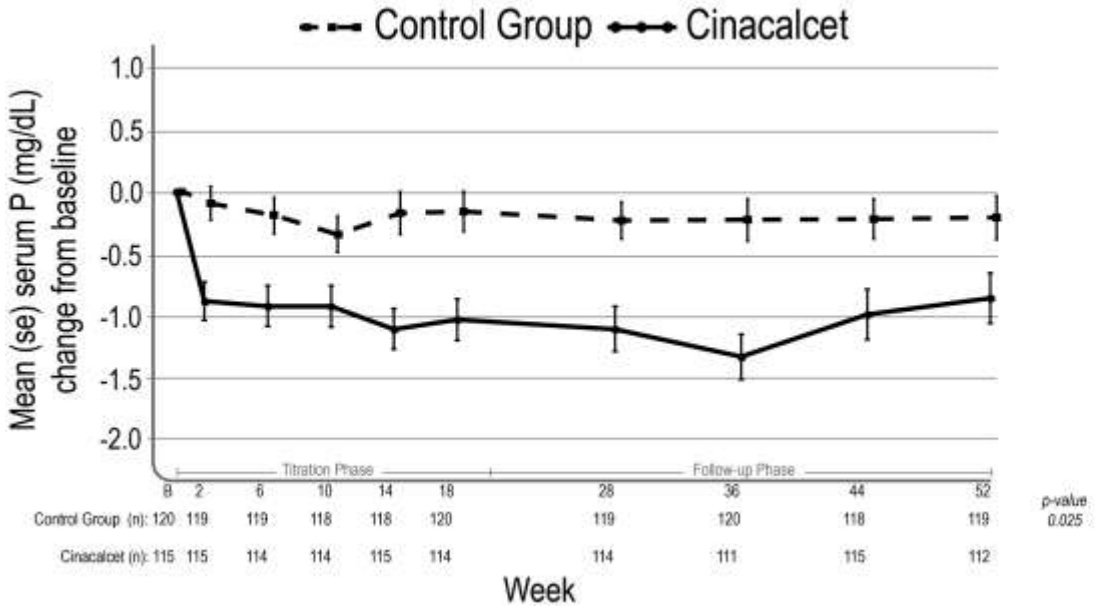
The ADVANCE study: a randomized study to evaluate the effects of cinacalcet plus low-dose vitamin D on vascular calcification in patients on hemodialysis

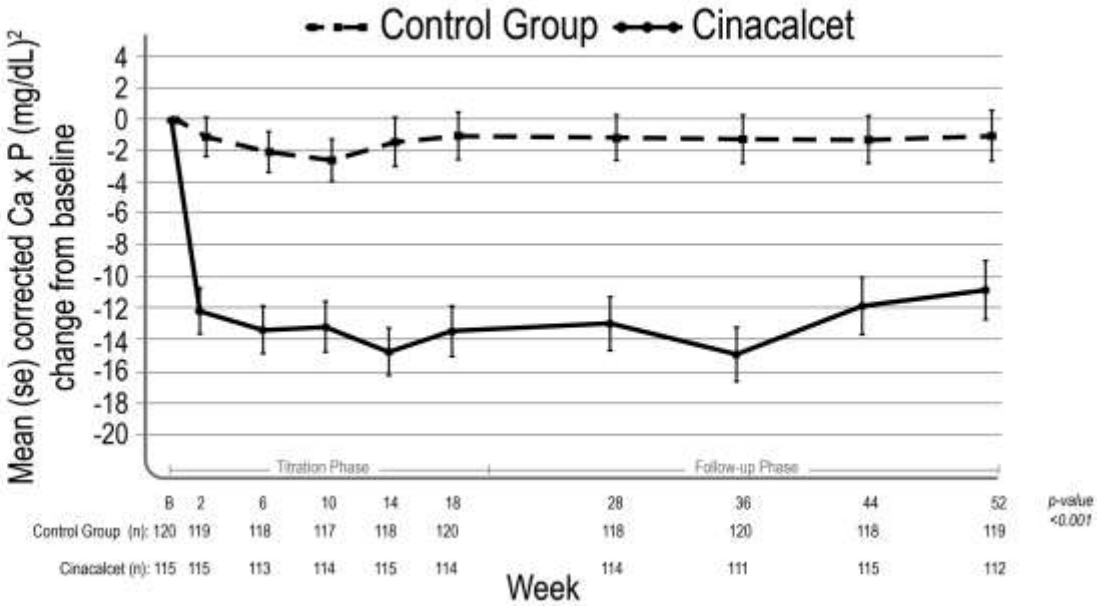


Nephrol Dial Transplant (2011) 26: 1327–1339



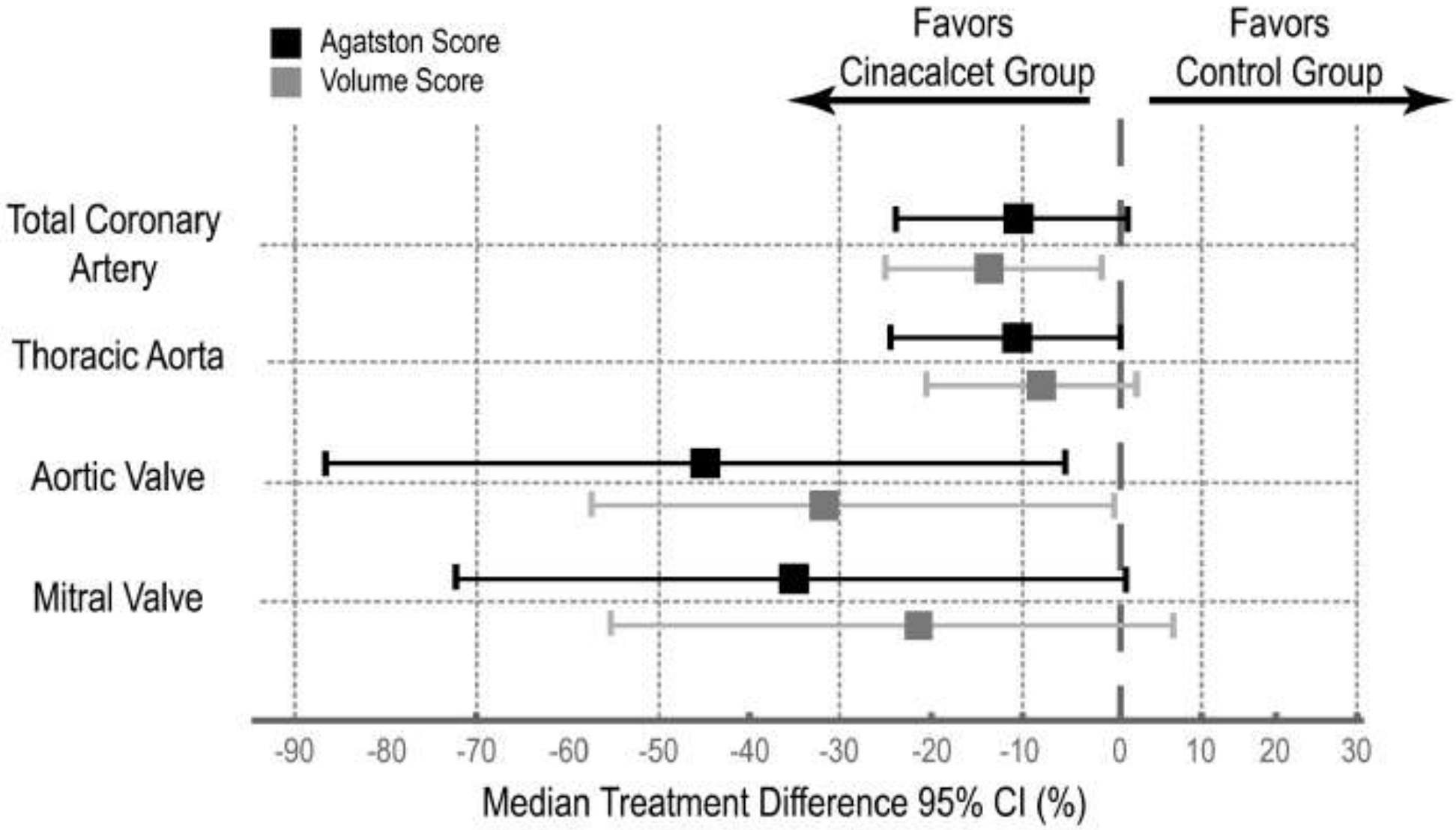






Nephrol Dial Transplant (2011) 26: 1327–1339

Cinacalcet reduces vascular calcification



Nephrol Dial Transplant (2011) 26: 1327–1339

EVOLVE Trial

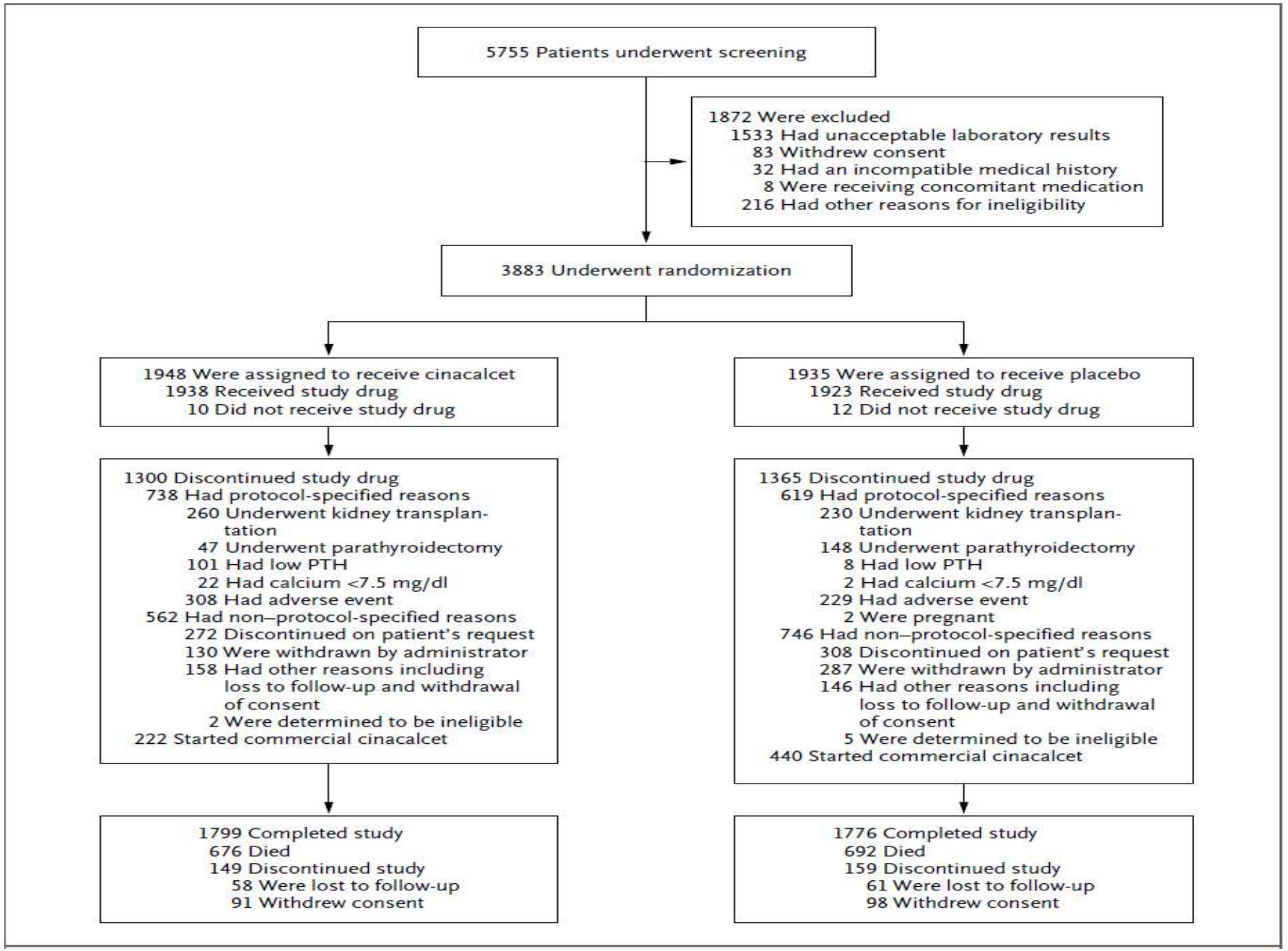
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

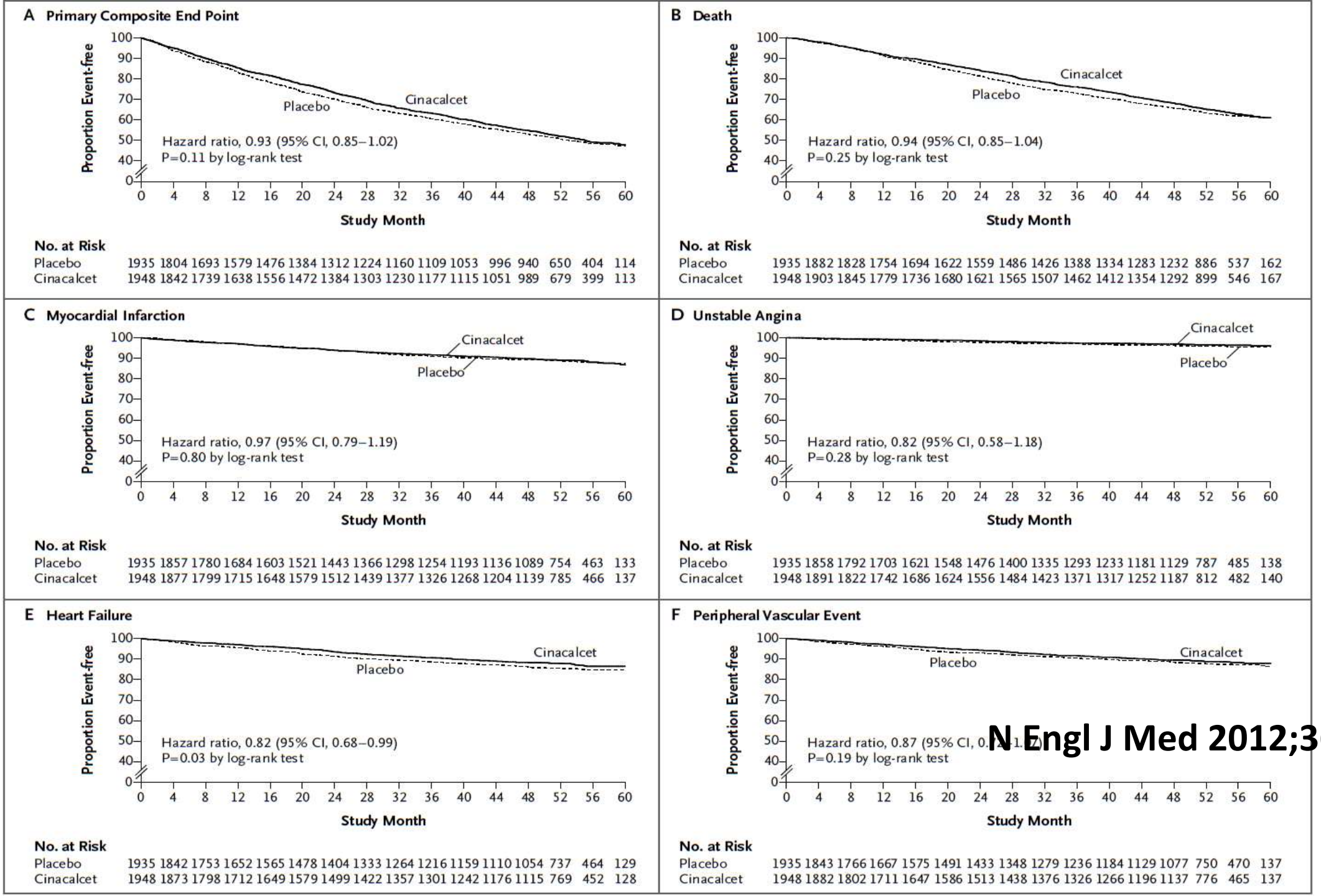
Effect of Cinacalcet on Cardiovascular Disease in Patients Undergoing Dialysis

The EVOLVE Trial Investigators*

N Engl J Med 2012;367:2482-94



N Engl J Med 2012;367:2482-94



N Engl J Med 2012;367:2482-94

3. FGF23-Klotho Axis

FGF23

- FGF23, a phosphaturic hormone produced by osteoblasts and osteocytes, and the associated co-receptor, Klotho, form a complex which is a major regulator of phosphorus metabolism.
- FGF23 decreases systemic phosphate exposure indirectly through modulation of vitamin D metabolism by reducing activation of vitamin D, and by enhancing its degradation.
- FGF23 inhibits synthesis and secretion of PTH from the parathyroid glands

Semin Dial 2007; 20: 302–308

- In patients at Stage 5D, the plasma concentration of FG23 is at least 20 times higher than the upper limit of the normal range in healthy individuals.

- This increase of FGF23 in CKD, particularly in Stage 5D, mainly reflects augmented synthesis of the agonist in the presence of resistance at the receptor level because Stage 5D is a condition of profound Klotho deficiency.

- Elevated FGF23 is an independent risk factor for ESRD in patients with relatively preserved kidney function and for mortality across the spectrum of CKD.

JAMA 2011; 305: 2432–2439

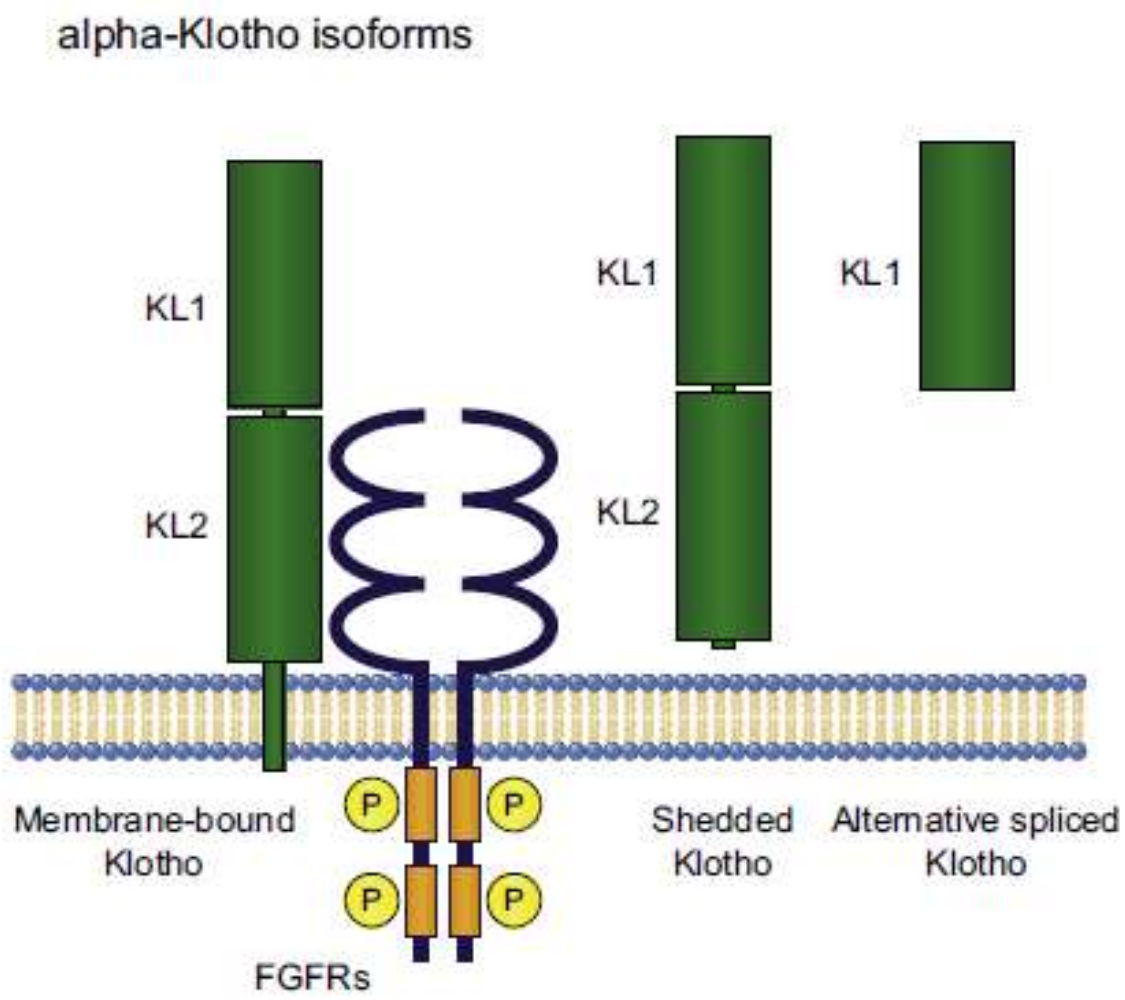
Klotho

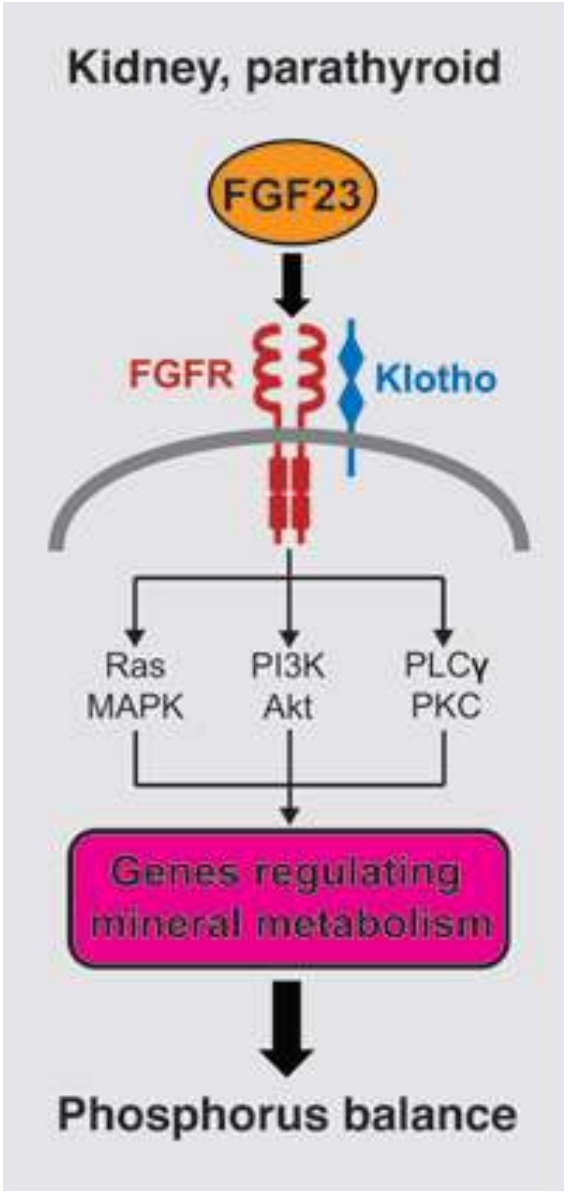
- α-Klotho (Klotho) gene and protein were discovered in 1997 by Kuro-o and co-workers.

- The name Klotho refers to Greek mythology, where Klotho is the one of the Fates, who is spinning the thread of life.

- Animal models, Klotho is associated with longevity.

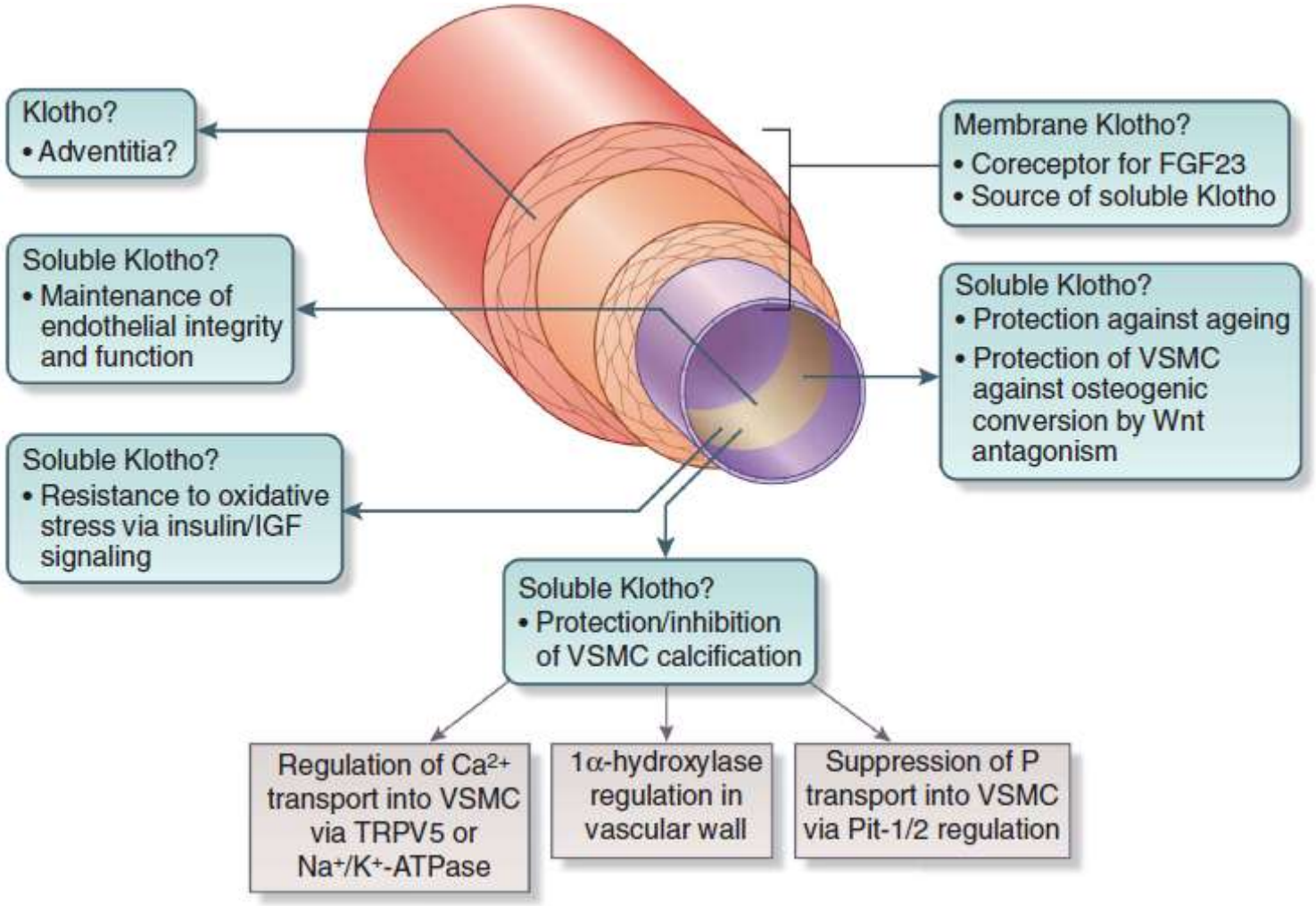
- Klotho exists in 2 forms, a membrane bound protein and as a soluble form.





Seminars in Nephrology, November2014, pp586–597

Vascular secrets of Klotho



Kidney International (2015) 87, 1089–1091

FGF23 & vascular calcification

http://www.kidney-international.org

clinical investigation

© 2013 International Society of Nephrology

Fibroblast growth factor 23 is not associated with and does not induce arterial calcification

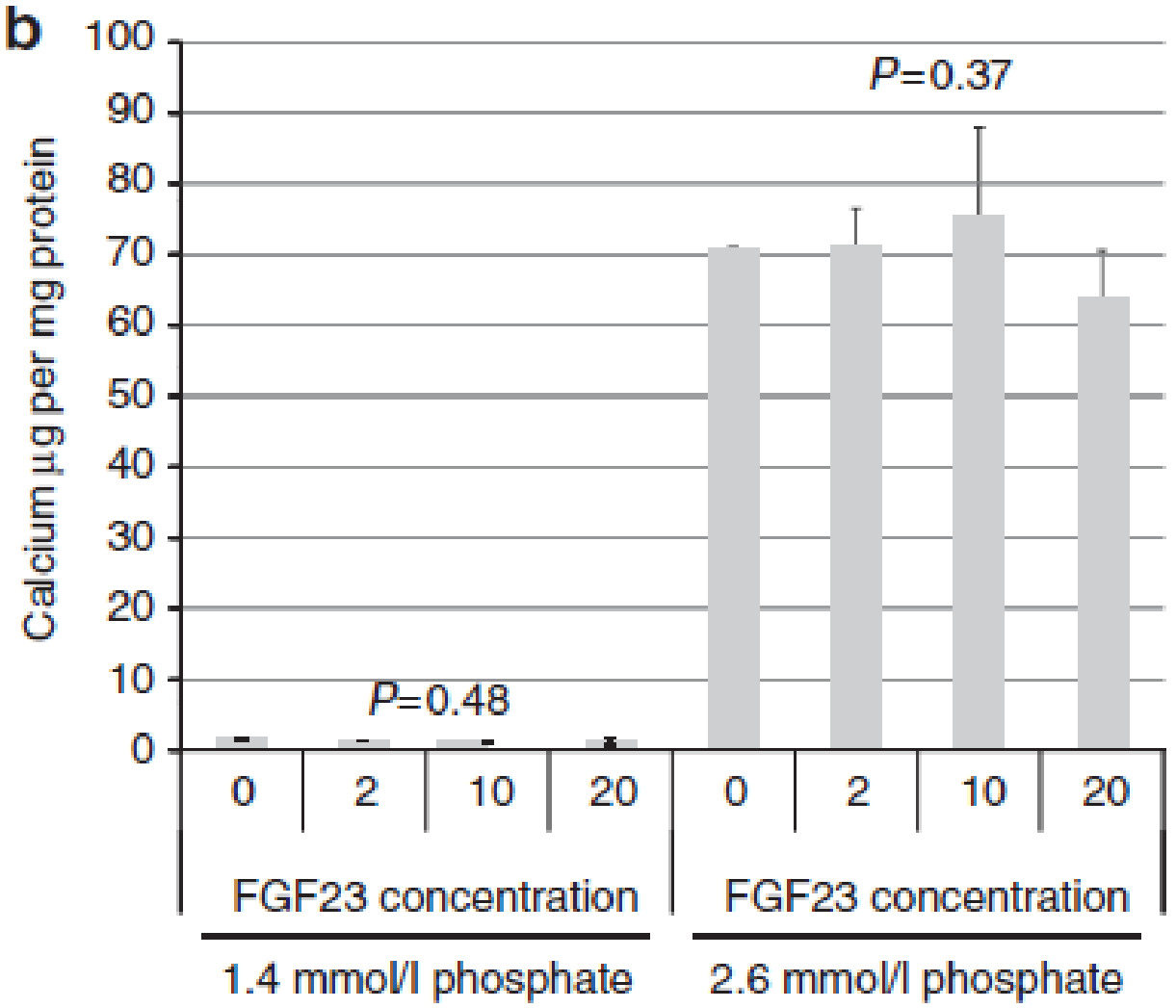
Julia J. Scialla[1,12], Wei Ling Lau[2,12], Muredach P. Reilly[3], Tamara Isakova[1], Hsueh-Ying Yang[4], Matthew H. Crouthamel[4], Nicholas W. Chavkin[4], Mahboob Rahman[5], Patricia Wahl[1], Ansel P. Amaral[1], Takayuki Hamano[6], Stephen R. Master[7], Lisa Nessel[6], Boyang Chai[6], Dawei Xie[6], Radhakrishna R. Kallem[3], Jing Chen[8], James P. Lash[9], John W. Kusek[10], Matthew J. Budoff[11], Cecilia M. Giachelli[4] and Myles Wolf[1] for the Chronic Renal Insufficiency Cohort Study Investigators

Association of FGF23 and PO4 with categories of coronary artery calcium (CAC) and thoracic aorta calcium (TAC)

Model[a]	Odds ratio for 1-unit increase in CAC category[b]	*P*-value	Odds ratio for 1-unit increase in TAC category[b]	*P*-value
ln FGF23 (per s.d.[c])				
−Phosphate	1.05 (0.93–1.20)	0.43	1.07 (0.94–1.21)	0.33
+Phosphate	1.02 (0.90–1.16)	0.74	1.06 (0.93–1.21)	0.38
Phosphate (per s.d.[c])				
−FGF23	1.29 (1.14–1.46)	<0.01	1.12 (0.98–1.27)	0.10
+FGF23	1.29 (1.13–1.46)	<0.01	1.11 (0.97–1.26)	0.13

Kidney International (2013) 83, 1159–1168

FGF23 did not induce calcification in cultured human VSMCs



Kidney International (2013) 83, 1159–1168

CRIC study

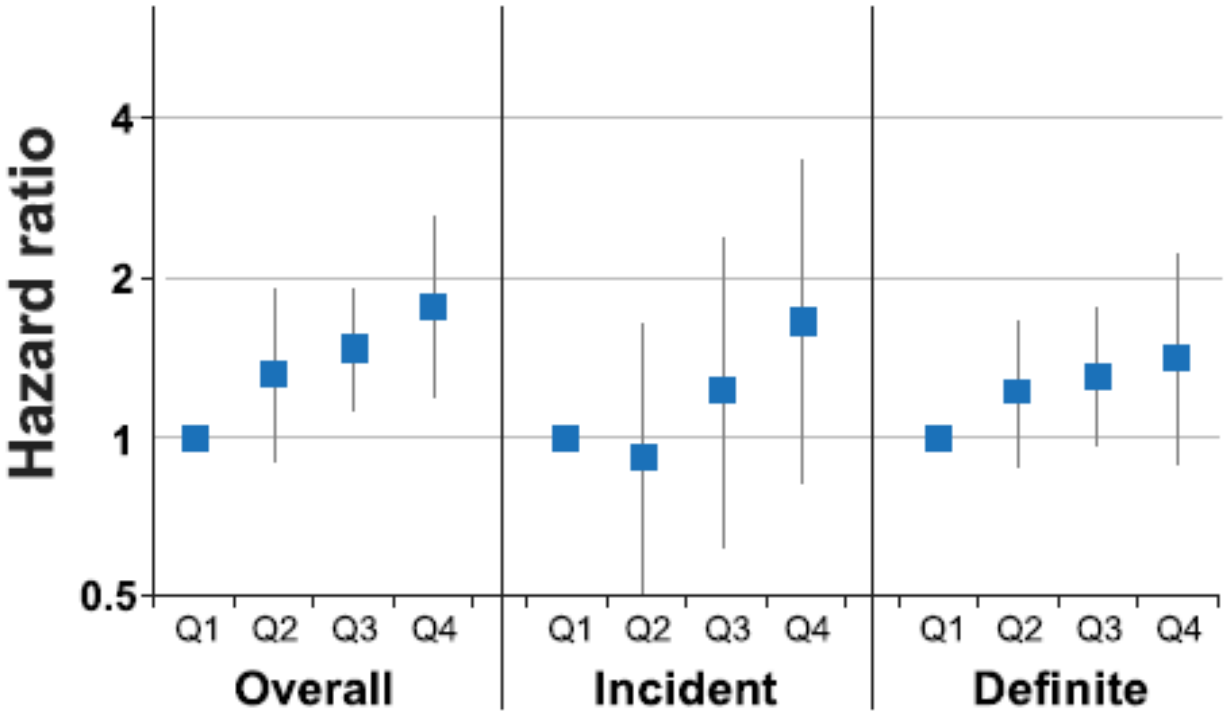
CLINICAL EPIDEMIOLOGY www.jasn.org

Fibroblast Growth Factor-23 and Cardiovascular Events in CKD

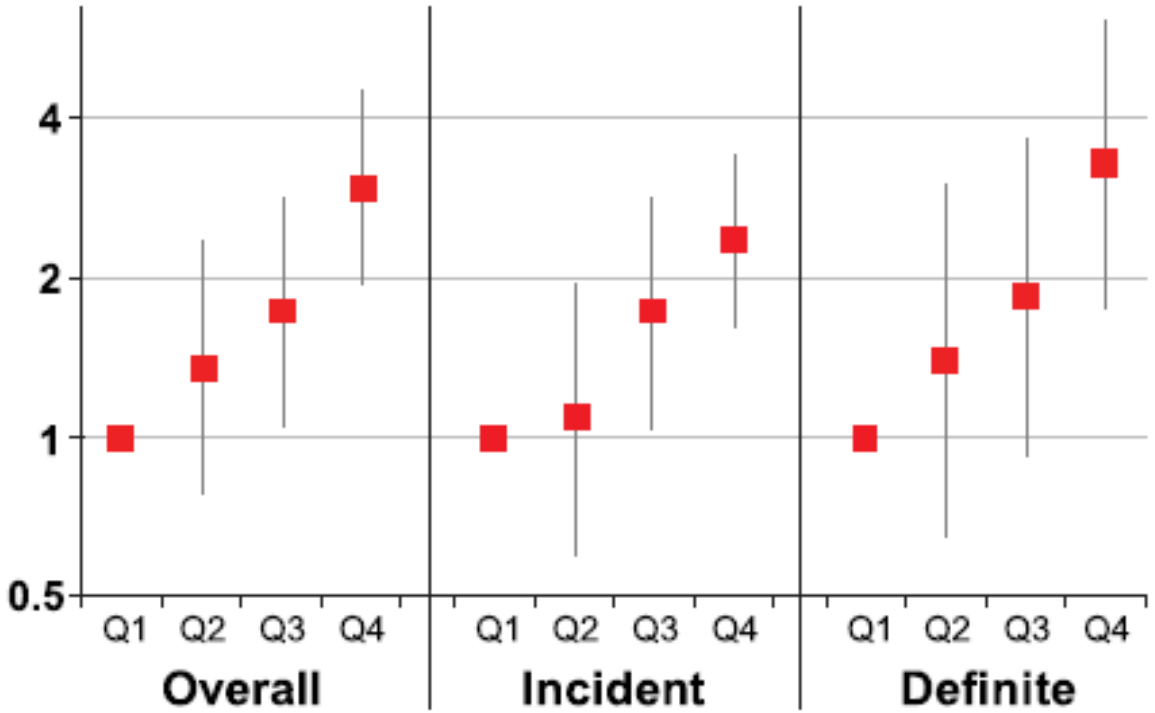
Julia J. Scialla,* Huiliang Xie,* Mahboob Rahman,† Amanda Hyre Anderson,‡ Tamara Isakova,* Akinlolu Ojo,§ Xiaoming Zhang,‡ Lisa Nessel, ‡ Takayuki Hamano,‡ Juan E. Grunwald,‡ Dominic S. Raj,‖ Wei Yang,‡ Jiang He,¶ James P. Lash,** Alan S. Go,†† John W. Kusek,‡‡ Harold Feldman,‡ Myles Wolf,* and the Chronic Renal Insufficiency Cohort (CRIC) Study Investigators

J Am Soc Nephrol 25: 349–360, 2014

FGF-23 is more strongly associated with congestive heart failure compared to atherosclerotic events

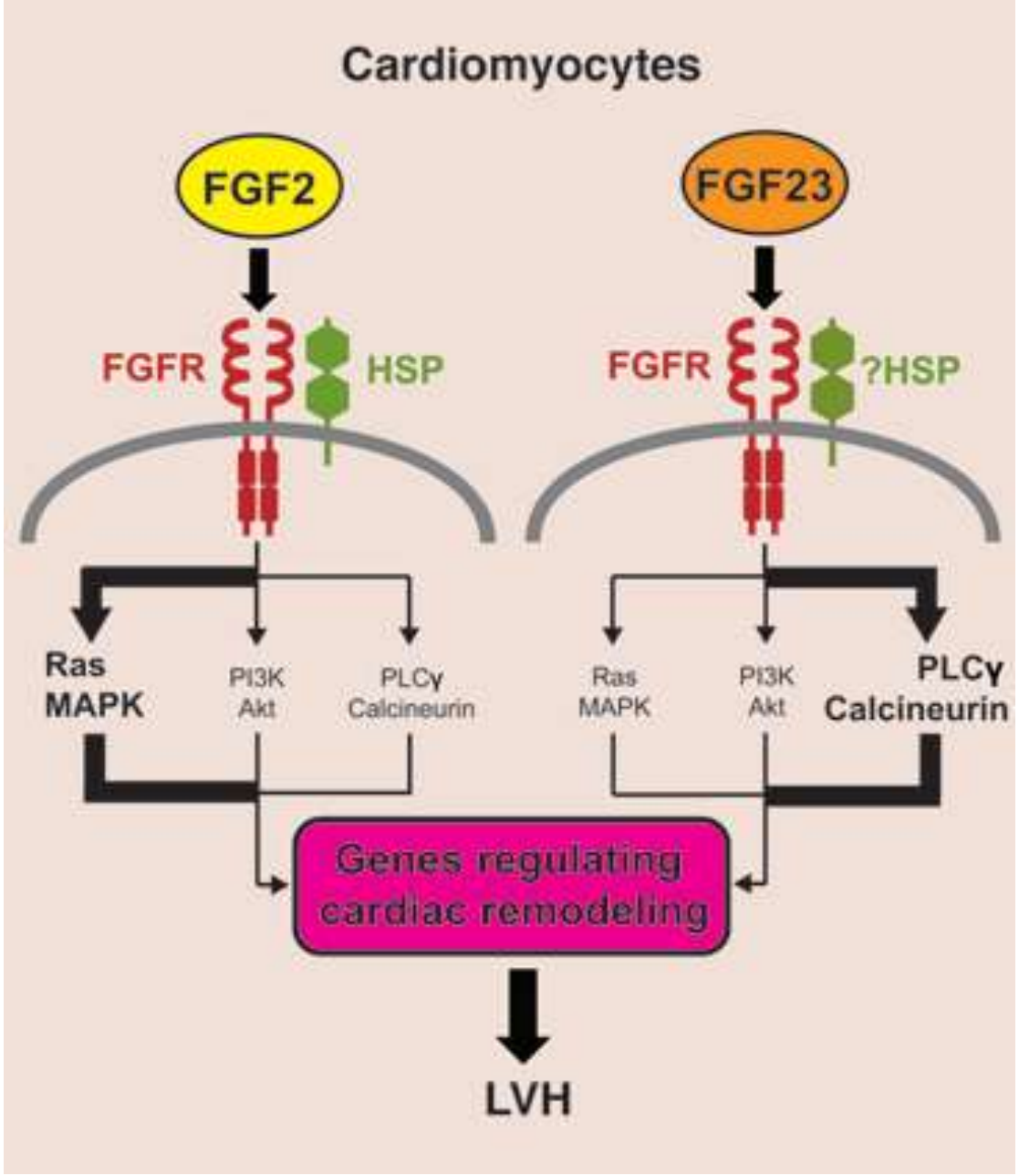


Atherosclerotic events



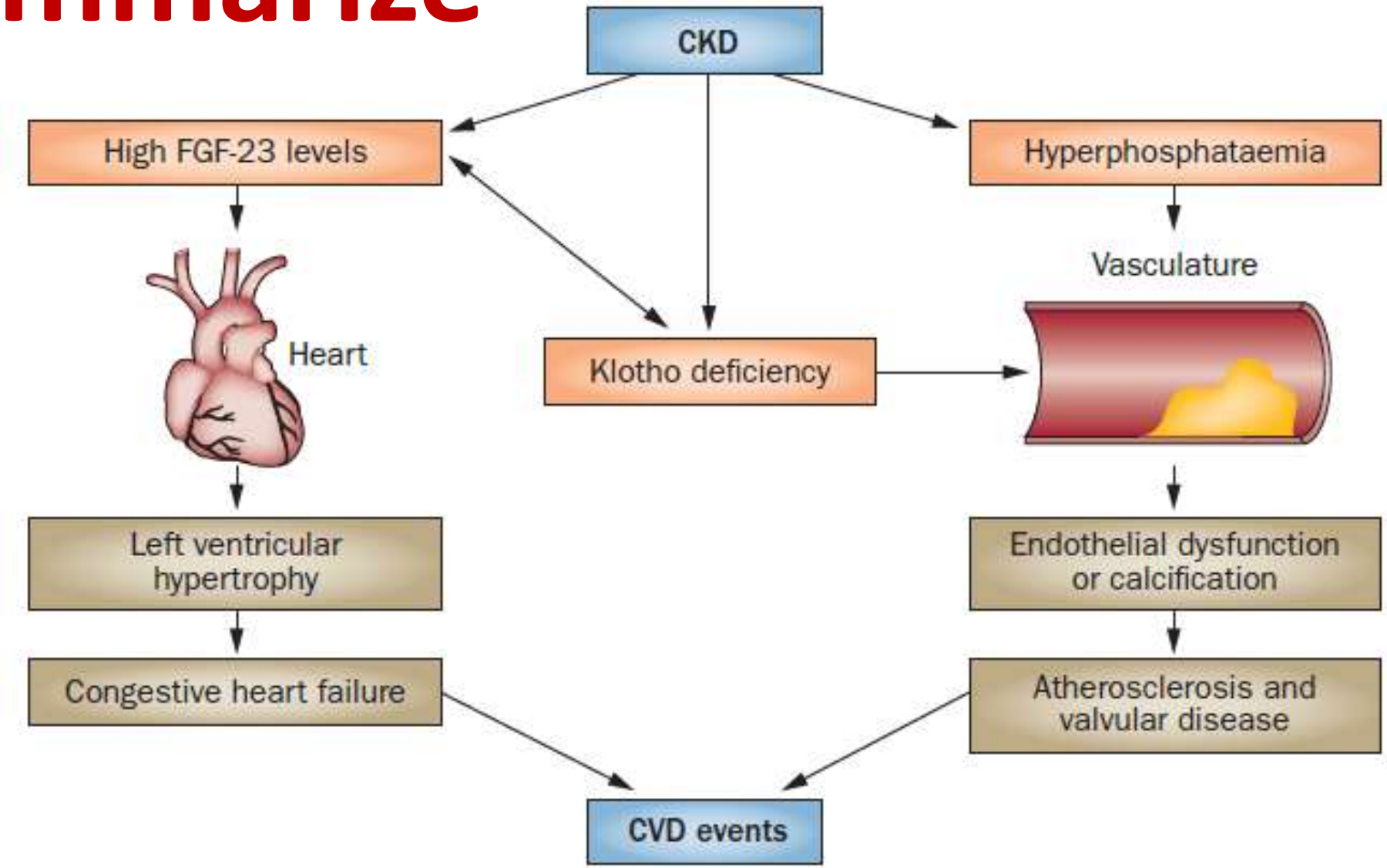
Congestive heart failure

J Am Soc Nephrol 25: 349–360, 2014



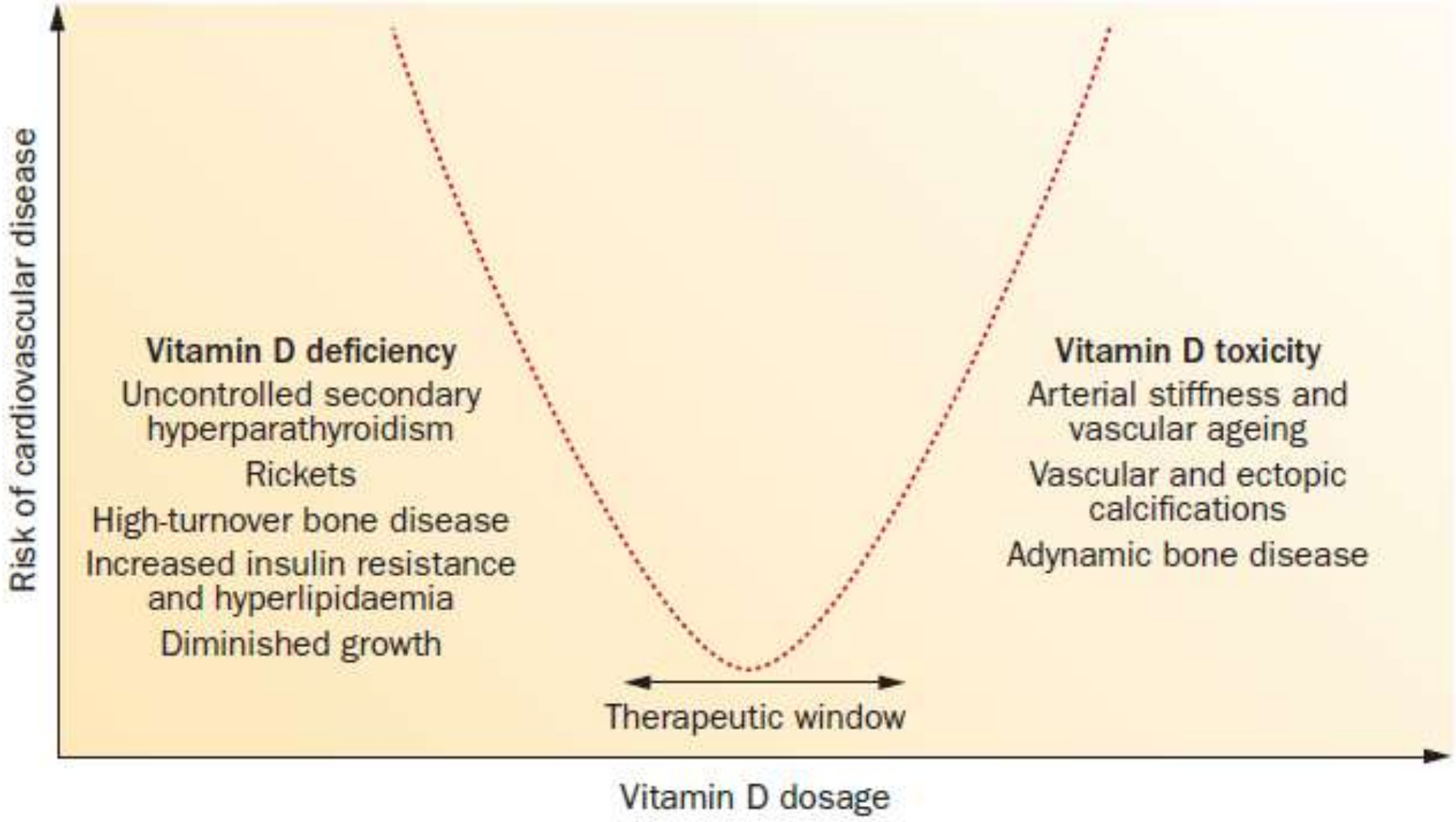
J Clin Invest. **2011;121(11):4393–4408**

Summarize



***Nat. Rev. Nephrol*. 10, 268–278 (2014)**

4. Vitamin D



***Pediatr. Nephrol.* 25 (2010) 2413–2430**

5. Fetuin-A

BASIC RESEARCH www.jasn.org

Fetuin-A Protects against Atherosclerotic Calcification in CKD

Ralf Westenfeld,* Cora Schäfer,† Thilo Krüger,* Christian Haarmann,* Leon J. Schurgers,‡ Chris Reutelingsperger,‡ Ognen Ivanovski,§ Tilman Drueke,§ Ziad A. Massy,‖ Markus Ketteler,¶ Jürgen Floege,* and Willi Jahnen-Dechent†

In conclusion, fetuin-A inhibits pathologic calcification in both the soft tissue and vasculature, even in the setting of atherosclerosis.

J Am Soc Nephrol 20: 1264–1274, 2009. doi: 10.1681/ASN.2008060572

6. Magnesium

REVIEWS

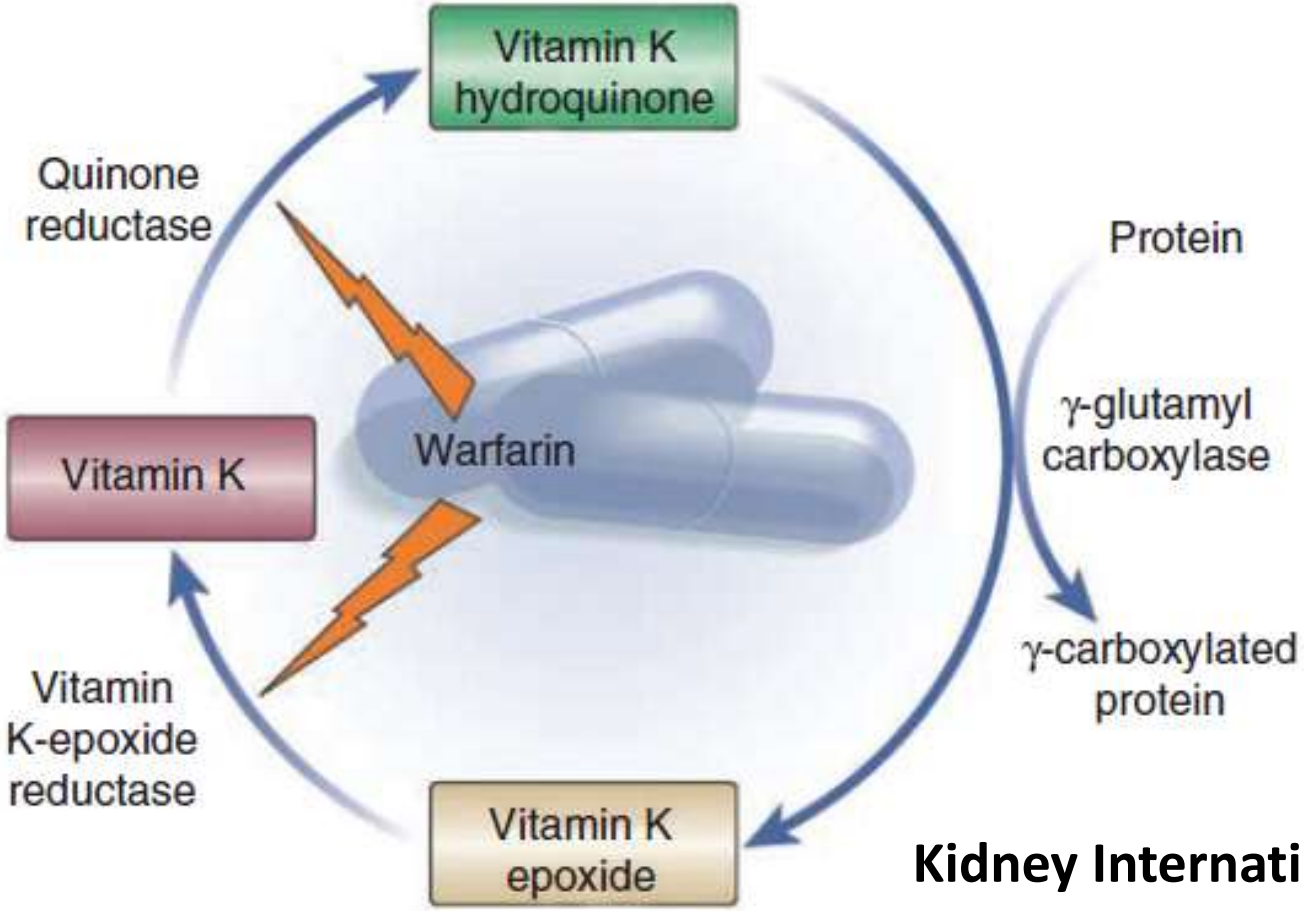
Magnesium and cardiovascular complications of chronic kidney disease

Ziad A. Massy and Tilman B. Drüeke

Nat. Rev. Nephrol. **11, 432–442 (2015)**

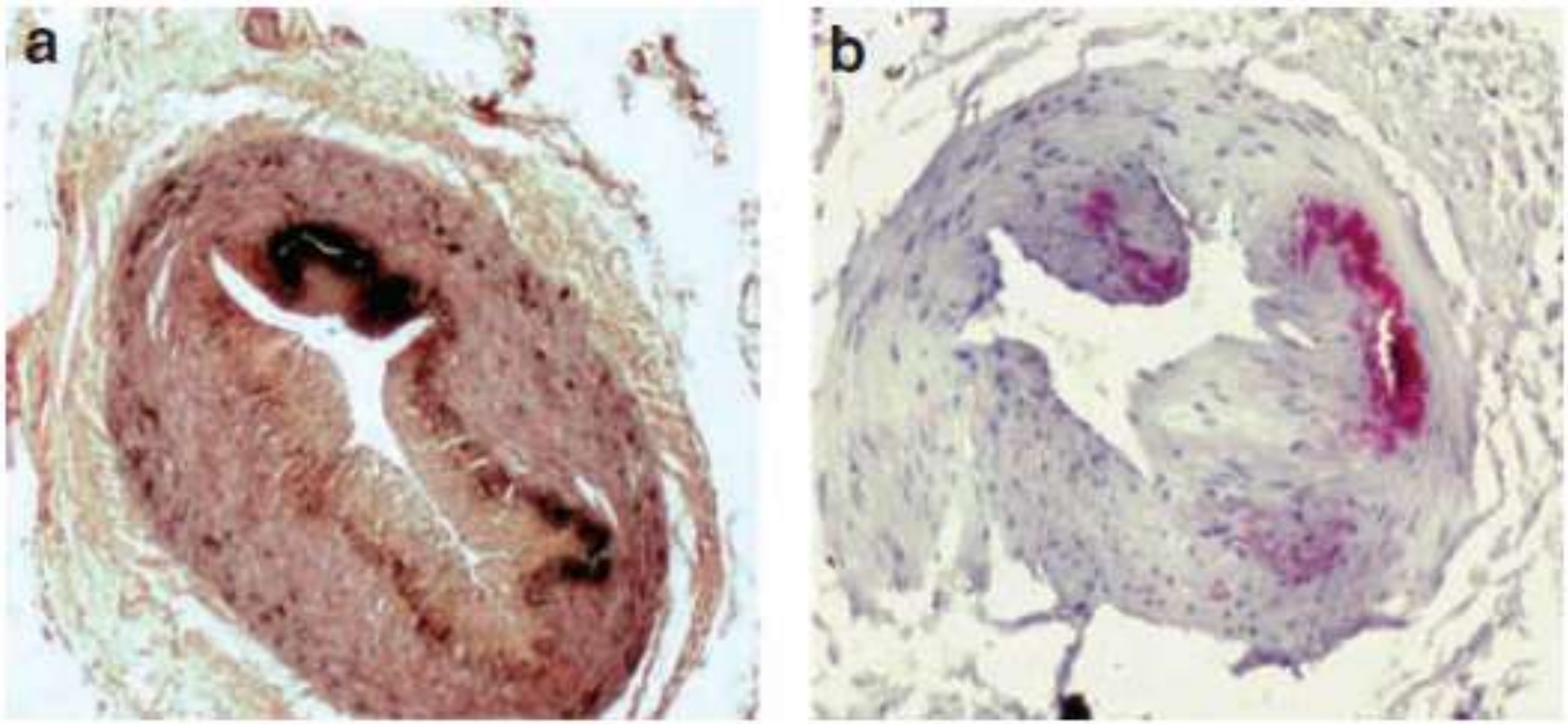
7. Vitamin K

- Vitamin K1 (phylloquinone): green leafy vegetables and vegetable oils
- Vitamin K2 (menaquinone): animals, bacteria, and fermented food such as cheese and natto.



Kidney International (2009) 76, 18–22

Human vascular calcification and ucMGP with warfarin



Kidney International (2009) 76, 18–22

Nature Reviews Nephrology published online 7 July 2015; doi:10.1038/nrneph.2015.87

Challenging the use of warfarin in patients on dialysis with atrial fibrillation

Georg Schlieper and Jürgen Floege

Study	Outcome	HR (95% CI)	Implication
Patients on dialysis			
Chan *et al.*[3]	Stroke and/or death	1.93 (1.29–2.90)	Against warfarin
Wizeman *et al.*[4]	Stroke and/or death (<65 years)	1.29 (0.45–3.68)	No benefit
	Stroke and/or death (65–75 years)	1.35 (0.69–2.63)	No benefit
	Stroke and/or death (>75 years)	2.17 (1.04–4.53)	Against warfarin
Winkelmayer *et al.*[5]	Ischaemic stroke	0.92 (0.61–1.37)	No benefit
	Haemorrhagic stroke	2.38 (1.15–4.96)	Against warfarin
Shah *et al.*[6]	Ischaemic stroke	1.14 (0.78–1.67)	No benefit
Patients undergoing RRT			
Olesen *et al.*[10]	Stroke and/or death	0.44 (0.26–0.74)	Favours warfarin
Bond *et al.*[2]	Death (high risk; CHA_2DS_2-VASc-score* ≥2)	0.85 (0.72–0.99)	Favours warfarin
	Death (low to intermediate risk; CHA_2DS_2-VASc-score 0–1)	1.36 (0.96–1.94)	No benefit

Conclusion

In weighing the risks of vitamin K antagonism in patients undergoing dialysis against the poorly documented benefits, we argue against the use of warfarin in patients with atrial fibrillation undergoing haemodialysis

VitaVasK trial

Nephrol Dial Transplant (2013) 0: 1–6
doi: 10.1093/ndt/gft459

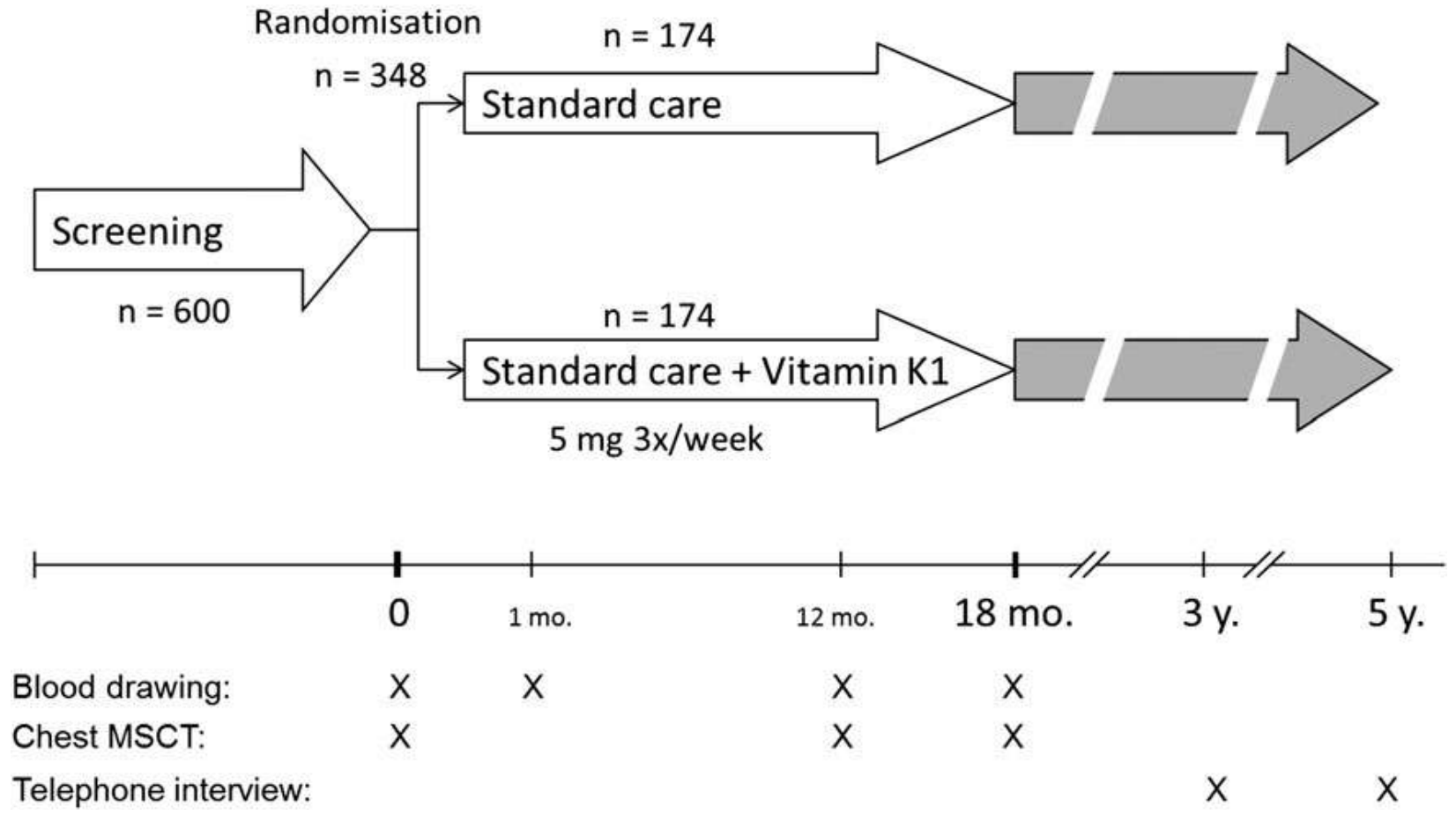
ndt
Nephrology Dialysis Transplantation

NDT perspectives

Vitamin K1 to slow vascular calcification in haemodialysis patients (VitaVasK trial): a rationale and study protocol

The total expected trial duration is 2.5 years. The recruitment of patients is scheduled to start in October 2013

Trial design



Nephrol Dial Transplant (2013) 0: 1–6

8. Other calcification inhibitors

Osteopontin (OPN)

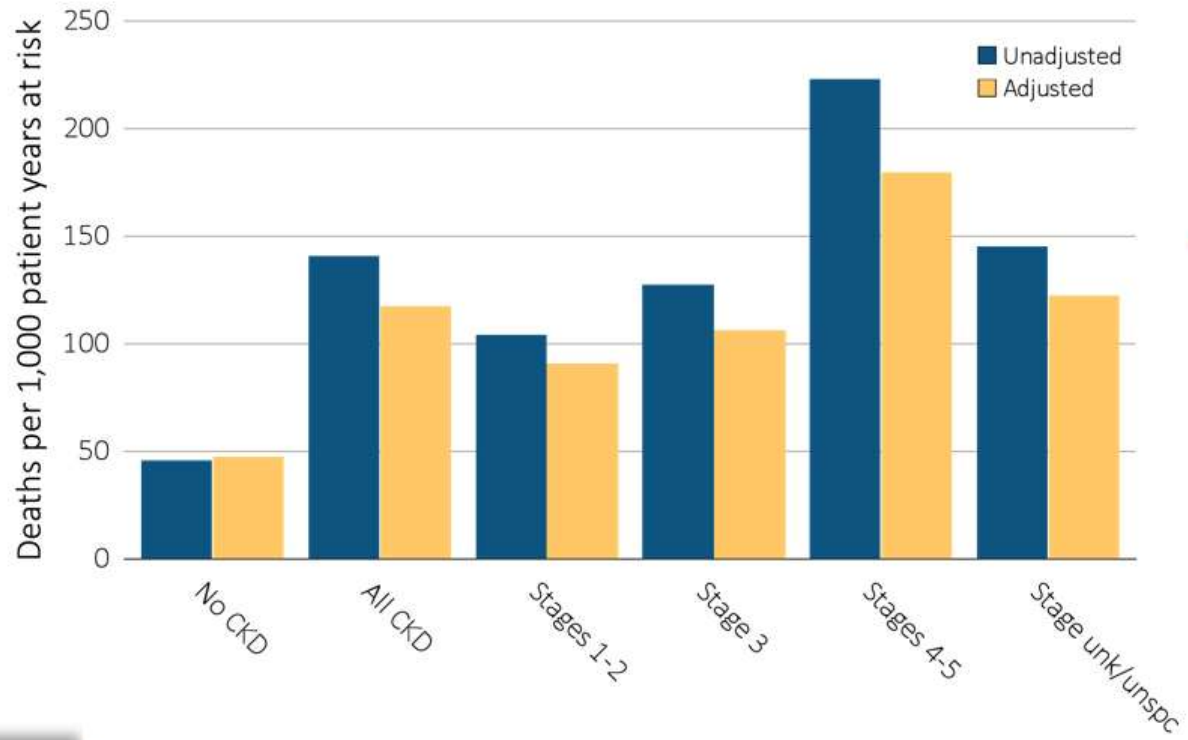
Osteoprotegerin (OPG)

Matrix Gla protein (MGP)

Conclusion

Don’t Forget

Mortality by CKD status and stage

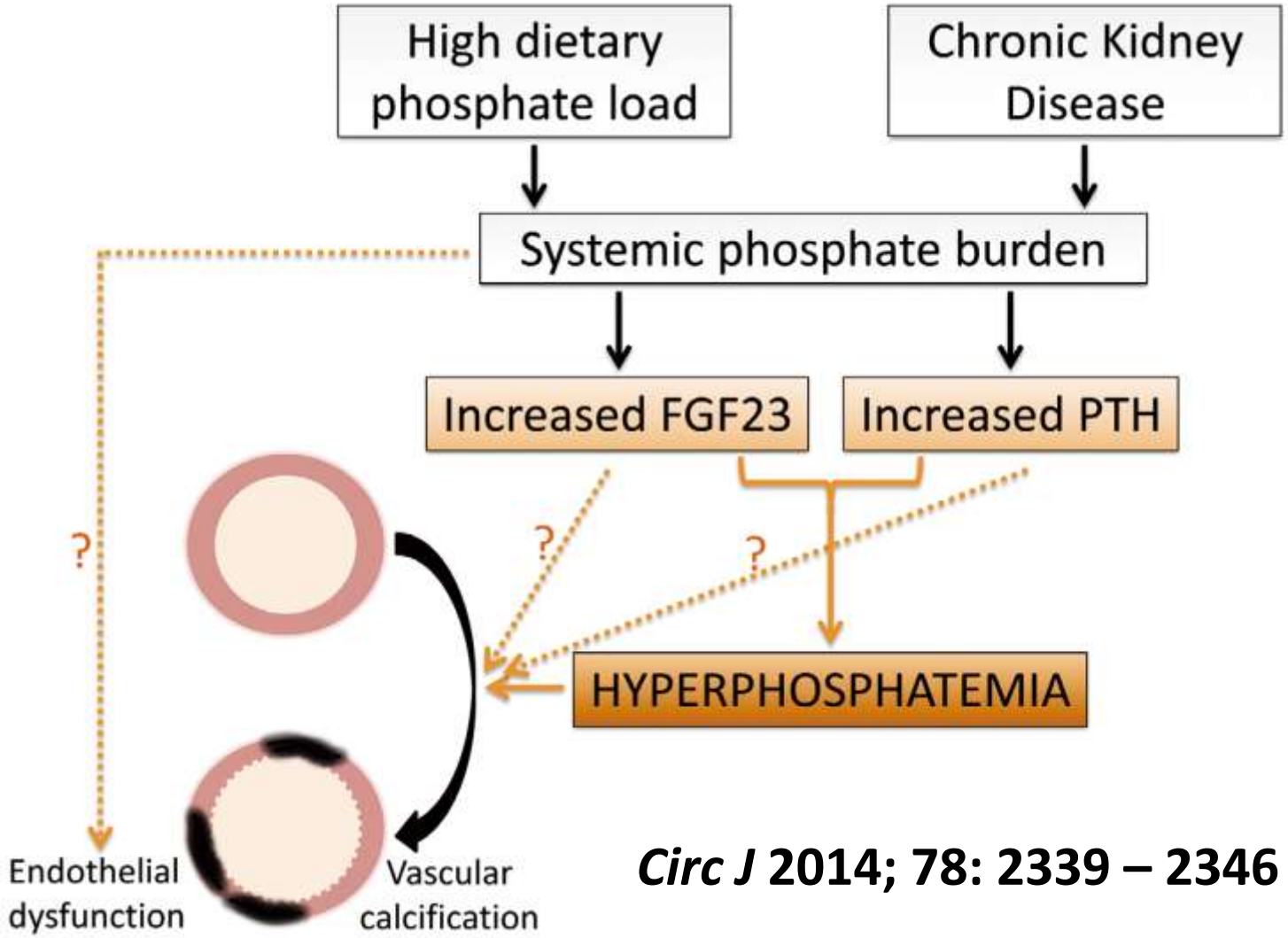


~40% Cardiac Causes

USRDS
UNITED STATES RENAL DATA SYSTEM

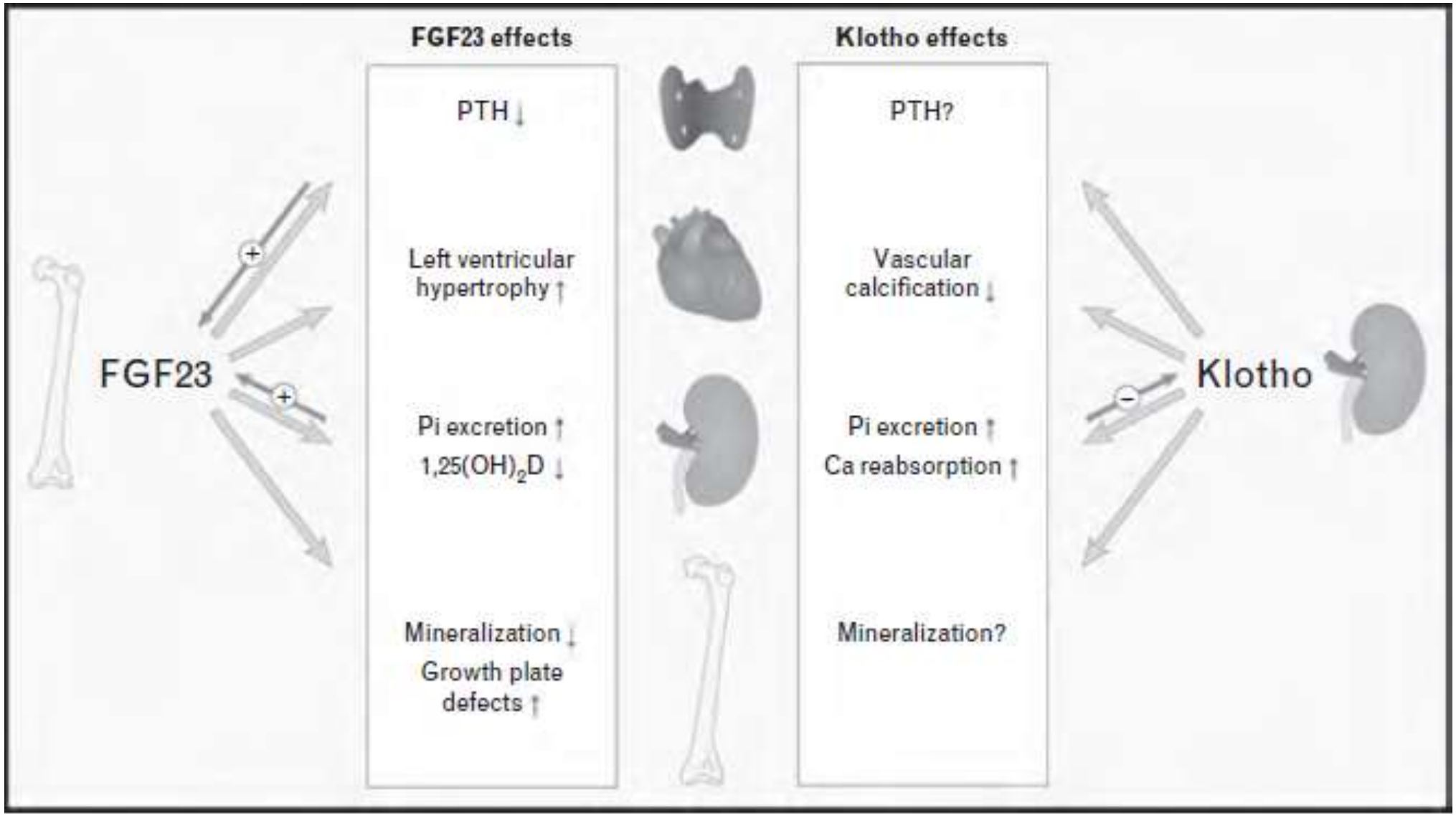
USRDS 2015 Annual Data Report

Don’t Forget
Potential role of phosphate in vascular damage



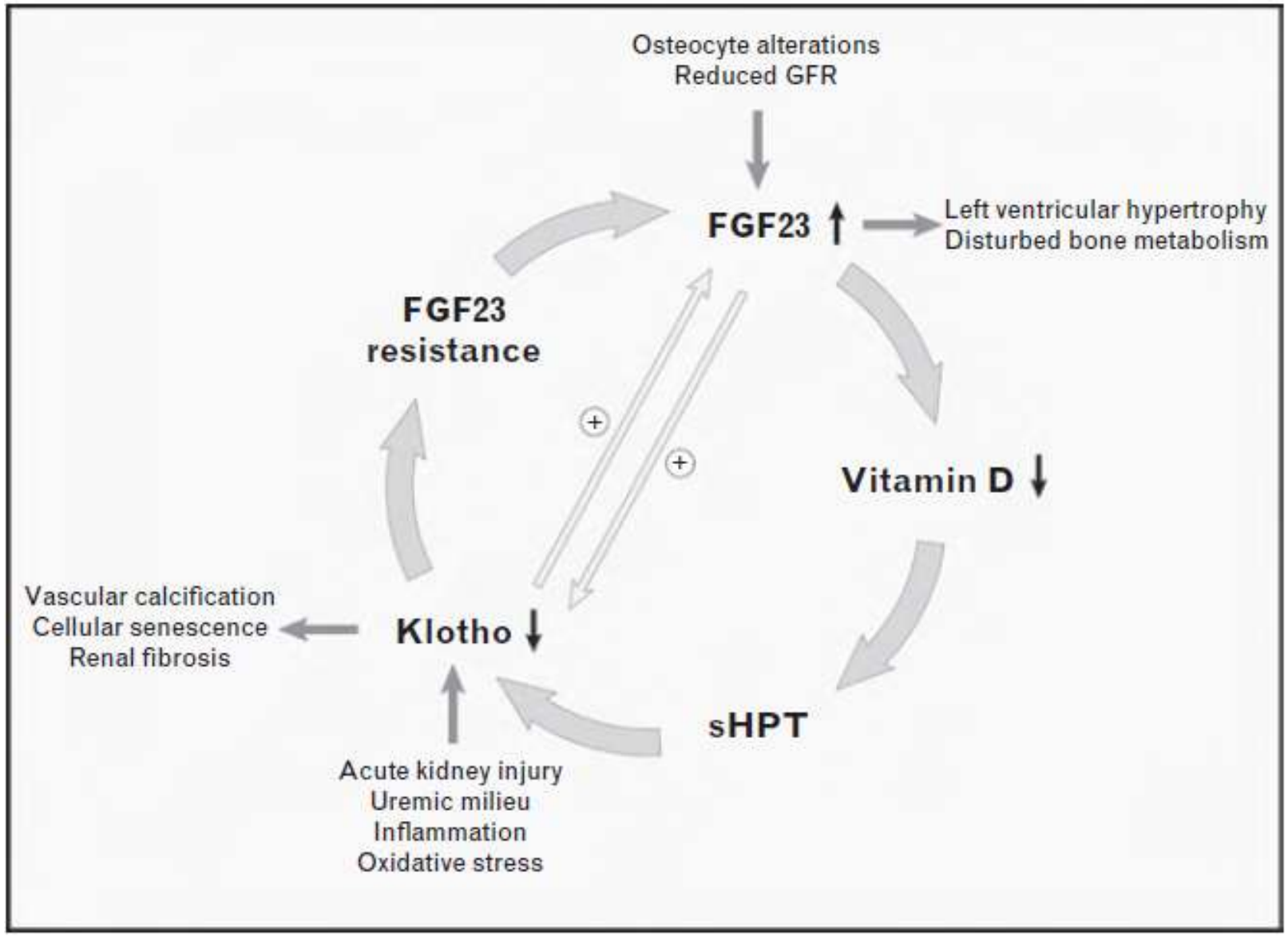
Circ J 2014; 78: 2339 – 2346

Don’t Forget



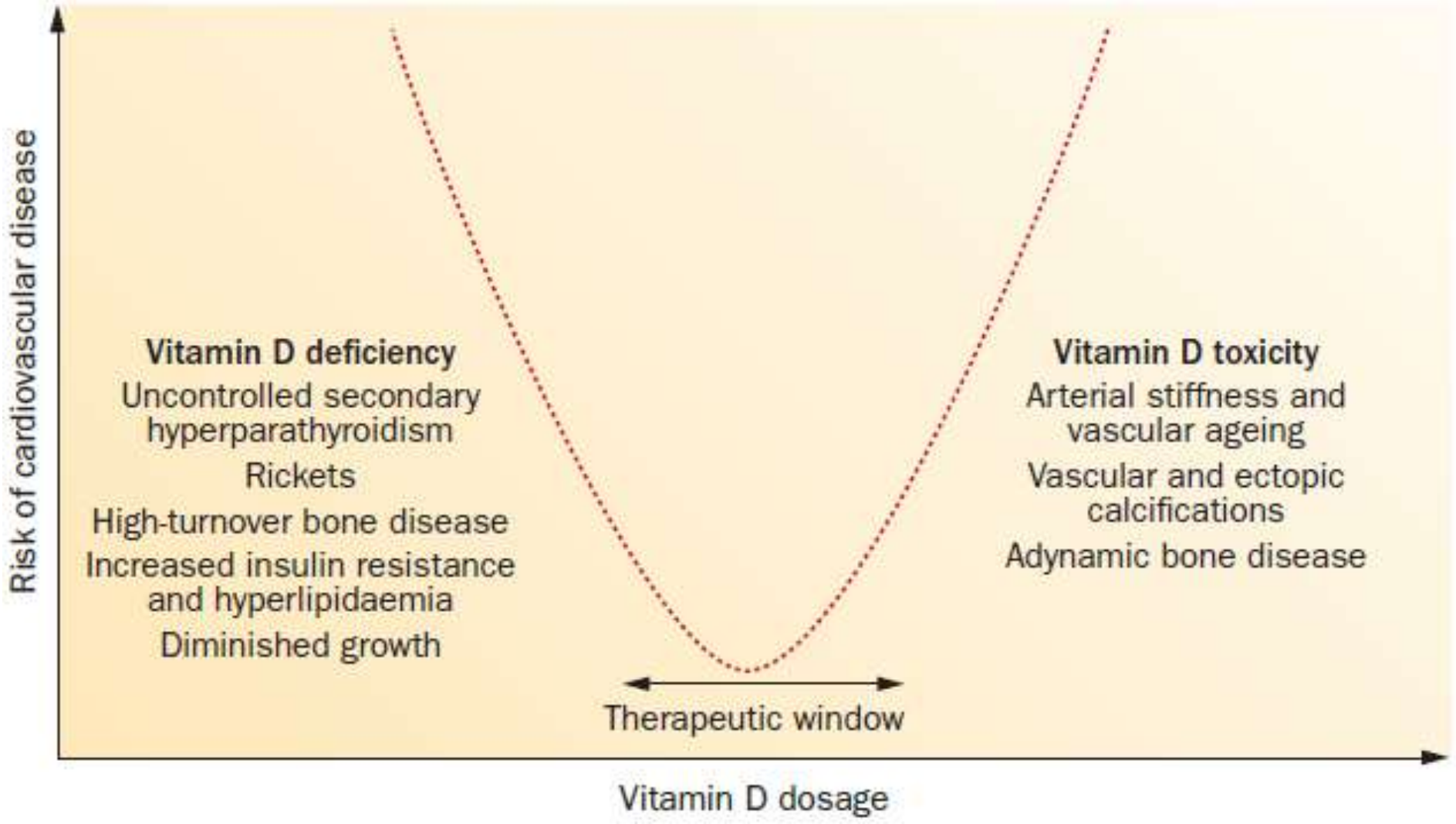
Curr Opin Nephrol Hypertens 2013, 22:397–404

Don’t Forget



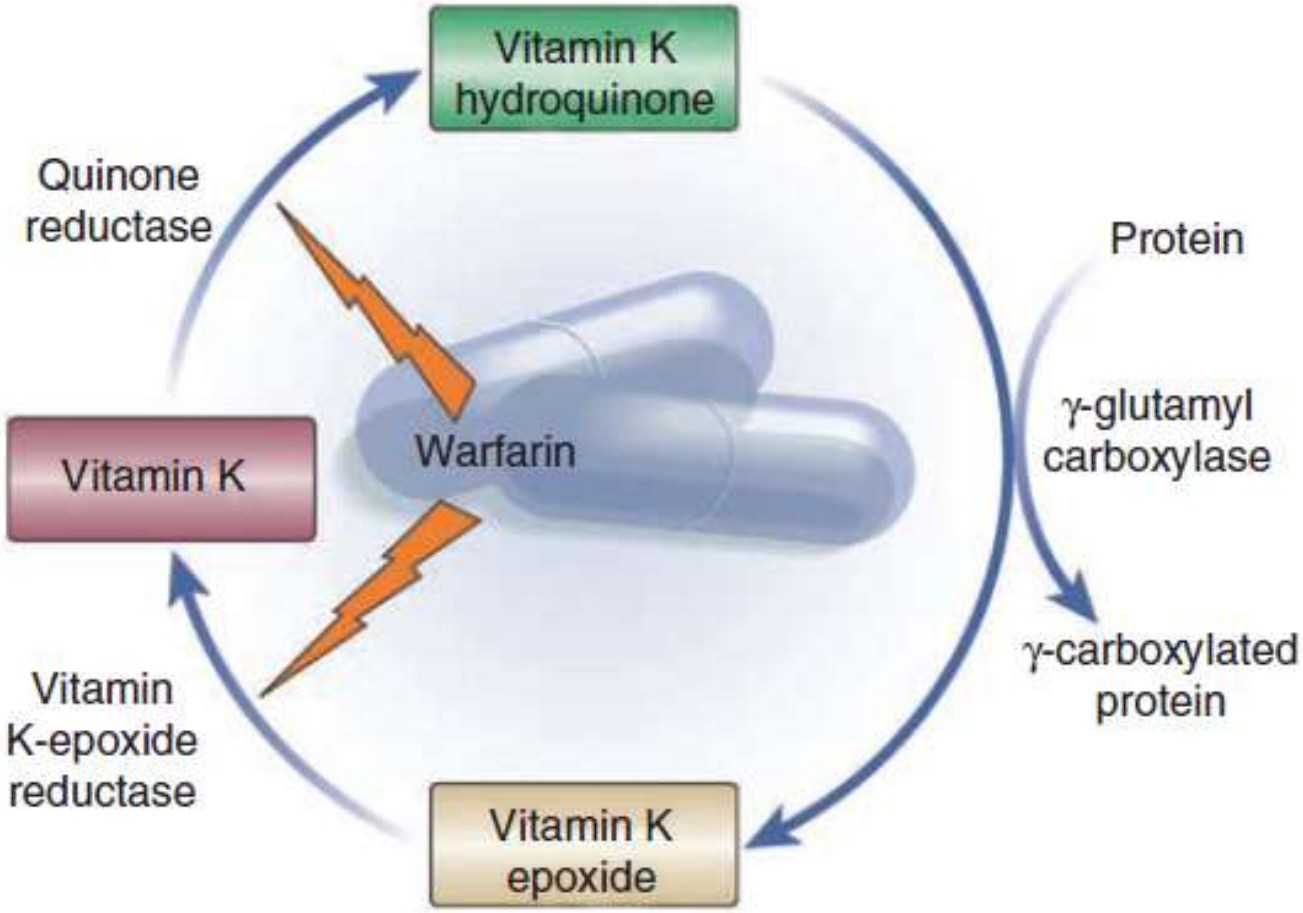
Curr Opin Nephrol Hypertens 2013, 22:397–404

Don’t Forget



***Pediatr. Nephrol.* 25 (2010) 2413–2430**

Don’t Forget



Kidney International (2009) 76, 18–22


Thank
you!